W 3
S86
v.12
SEP 20 1927
Medical Lib.

ALLERGY NUMBER—INDEX NUMBER

Vol. XII SEPTEMBER, 1927 No. 12

The Journal of Laboratory and Clinical Medicine

WARREN T. VAUGHAN, M.D., Editor-in-Chief
Medical Arts Building
Richmond, Va.

ASSOCIATE EDITORS

Pharmacology
DENNIS E. JACKSON, M.D.
University of Cincinnati, Cincinnati

Pathology
PAUL G. WOOLLEY, M.D.
Los Angeles

Physiology
J. J. R. MACLEOD, M.B.
University of Toronto, Toronto

Tuberculosis
GERALD B. WEBB, M.D.
Cragmor Sanatorium, Colorado Springs

Clinical Pathology
W. C. MacCARTY, M.D.
Mayo Clinic, Rochester, Minn.

HAROLD D. CAYLOR, M.D.
Mayo Clinic, Rochester, Minn.

Biochemistry
VICTOR C. MYERS, Ph.D.
Western Reserve University, Cleveland

Experimental Medicine
RUSSELL L. HADEN, M.D.
University of Kansas, Rosedale

Immunology
JOHN A. KOLMER, M.D.
University of Pennsylvania, Philadelphia

ROBERT A. KILDUFFE, M.D.
Atlantic City, N. J.

Bacteriology
A. PARKER HITCHENS, M.D.
Bureau of Science, Manila, P. I.

Surgery
DEAN LEWIS, M.D.
Johns Hopkins University, Baltimore

Internal Medicine
GEORGE R. HERRMANN, M.D.
Tulane University, New Orleans

Official Organ of the American Society of Clinical Pathologists

PUBLISHED BY THE C. V. MOSBY COMPANY, 3523-25 PINE BLVD., ST. LOUIS.
Entered at the Post Office at St. Louis, Mo., as Second Class Matter.

The New Fifth Revised Edition of a Popular Book

Physiology and Biochemistry in Modern Medicine

Over 1100 pages, 6½x9½, with 250 illustrations, including half-tones and line drawings, and 9 color plates. Price, silk cloth binding, $11.00.

BY J. J. R. MACLEOD, M.B., LL.D., D.Sc., F.R.S.

Professor of Physiology in the University of Toronto; Formerly Professor of Physiology in the Western Reserve University.

Assisted by Roy G. Pearce, A. C. Redfield, N. B. Taylor, J. M. D. Olmsted, and by others.

Freas Incubator No. 26

Your Incubator Must be Accurate

Just as with your laboratory worker your incubator must be capable of performing the assigned tasks accurately.

Accuracy in an incubator is its ability to maintain the temperature constant continuously.

This is why the Freas Incubators are used in the leading laboratories.

The Thermo Electric Instrument Co.

1215 South Grove Street, Irvington, N. J.

FREAS

ELECTRIC INCUBATORS

The Journal of Laboratory and Clinical Medicine

VOL. XII ST. LOUIS, MO., SEPTEMBER, 1927 NO. 12

CLINICAL AND EXPERIMENTAL ALLERGY

STUDIES IN HYPERSENSITIVENESS

XXIX. ON THE INFLUENCE OF HEREDITY IN ATOPY*

BY ARTHUR F. COCA,† NEW YORK CITY

I WANT to preface my remarks with a very brief review of the salient facts concerning atopic hypersensitiveness, which may be considered established and with which most of you are well acquainted.

1. Atopy (comprising provisionally bronchial asthma and hay fever) is an inherited affection, as has been shown by Dr. Cooke and his associates, and confirmed by June Adkinson.

2. In the blood of atopic individuals exhibiting a specific cutaneous reaction, sensitizing bodies specifically related to the excitant are nearly always demonstrable. These sensitizing bodies have been called atopic reagins, a designation that distinguishes them from the anaphylactic antibodies.

3. Both anaphylactic antibodies and atopic reagins can be produced by human beings, conceivably by the same individual.

4. A human individual that produces only anaphylactic antibodies to an antigen is not atopically sensitive to that antigen.

5. The atopic reagins are incapable of conferring anaphylactic hypersensitiveness on the classical test animal (the guinea pig).

Almost every aspect of the subject of human hypersensitiveness presents a question for which no answer has been found, and one of the first of these is, what shall be included in the atopic group; can this group be sharply defined or not?

*Abstracted from an address delivered before the American Association for the Study of Allergy, Washington, D. C., May 16, 1927.

†From the Department of Bacteriology and Immunology, Division of Immunology, in Cornell University Medical College and the New York Hospital.

The chief criterion of an atopic hypersensitiveness has been its dependence upon the hereditary influence. Under this criterion, atopy obviously comprises bronchial asthma and hay fever. To these may possibly be added certain forms of drug and food idiosynerasy, but this question evidently calls for more study. It must not be forgotten that not all forms of natural human hypersensitiveness are subject to the atopic hereditary factor; for example, ordinary serum disease and dermatitis venenata.

A second criterion of atopy was thought, at first, to have been found in the atopic reagins demonstrable with the technic of local passive transfer, but since Rackemann has shown that the serum of worm-infested individuals is capable of passively sensitizing normal skin to worm extracts, this property of atopic serum cannot be used for classificatory purpose. Rackemann's observations have been amply confirmed by Walzer's associate, M. Brunner.

The atopic group is thus left with only one clear bond of union, namely, the bond of heredity.

The demonstration of the familial nature of atopy was made by Cooke and his associates upon two lines of evidence. These writers showed, first, that the percentage of atopic children was greatest (69.5) in families subject to a bilateral hereditary influence, and least (41.1) in those in which the family history was negative for atopic conditions. They also showed that the age of onset of the atopic symptoms is distinctly affected by inheritance. This is seen in the fact that, under a bilateral familial influence, 72 per cent of the affected offspring begin to exhibit symptoms before the tenth year of age, whereas only about 35 per cent of the affected children, that are subject to a unilateral familiar influence, have begun to show symptoms by that age; this percentage falls to 20 among those children whose atopic family history is negative.

The consequences of this evidence seem not to have been fully recognized. The first of these is the simple corollary that, under conditions that permit adequate contact with the excitant, the date of onset of atopic symptoms is determined, in some way, by hereditary influence, *for each atopic individual*. In other words, the date at which an atopic individual will begin to experience atopic symptoms is usually predetermined in the inheritance. This principle is in harmony with the well-known fact that many atopic persons have been in constant or annual contact with the excitant (pollens, animal danders) for years previous to the onset of symptoms.

To the question as to the way in which the establishment of atopic hypersensitiveness is influenced by heredity, the first natural suggestion is the one that has been most favored, and which is used dogmatically in a recent issue of a semipopular scientific magazine. This suggestion assumes an abnormal permeability of the surface membranes in the hypersensitive individuals. The theory is greatly handicapped with the necessity of admitting that the abnormal permeability in many persons must be exhibited to only one member of a group of similar excitants (a single pollen atopen or a single animal or vegetable protein). Such a specificity of permeability could not be assumed without some experimental evidence.

The studies of Anderson and Schloss, however, and those of Walzer, which have revealed an unsuspected normal permeability of the gastrointestinal tract to various common proteins (milk, egg, nut, fish, pollen) finally remove the hypothesis from the field.

Anderson and Schloss have shown that the passage of foreign protein through the intestinal wall of normal babies results in the production, by these individuals, of antibodies (precipitating and anaphylactic); yet these individuals exhibited no signs of clinical sensitiveness. Moreover, it is a matter of everyday knowledge that, even the repeated injection of large quantities of foreign protein (horse serum) does not induce atopic hypersensitiveness.

Thus it is seen, on the one hand, that atopy is not controlled through hereditary differences in permeability of surface membranes, and, on the other hand that, in the absence of the hereditary factor, contact with atopic excitants, parenteral and prolonged, is not a sufficient cause of atopy.

When the atopic reagins were discovered and the reaginogenic organ was recognized as distinct in the human being from that which produces precipitin and anaphylactic antibody, we thought that this function was, of course, strictly subject to atopic inheritance. In other words, we supposed that the reaginogenic organ functions only in atopic individuals. This seemed indicated by the specificity of the reagins and their constant presence in the blood of asthmatics and hay fever subjects presenting a positive skin reaction. But, as we have said, Rackemann has shown that the serum of worm-infested individuals is capable of passively sensitizing the normal human skin to worm extracts; and this observation has since been amply confirmed by M. Brunner.

Rackemann's findings seem to show that the reaginogenic organ is not confined to atopic individuals; it seems to be present in all individuals and responds specifically to substances in worms.

When, however, the reaginogenic organ of the *nonatopic* person is stimulated by the worms to produce reagins, the constitutional hypersensitiveness of atopy seems not to be thereby induced; this is shown by observations of Walzer and Brunner, which these experimenters have permitted me to mention in advance of their formal publication. Three of the worm-sensitive persons were subject to asthma due to some excitant other than the worms, which were not present, at the time, in the intestinal tract, and the injection of a certain quantity of worm extract into these three persons caused a constitutional reaction. Similar injections in worm-sensitive but nonatopic persons, on the contrary, caused no symptoms.

While admitting the probable identity of the antiworm reagins of Rackemann with the atopic reagins, one must not overlook the fact that the production of these bodies against typical atopens has not been demonstrated in nonatopic persons.

In several papers in which we have discussed the atopic reagins, we have emphasized the superior importance of the "tissue factor," that is, the shock organ in atopy. The determining importance of the shock organ is evident in the well-known fact that, although reagins are present in the blood in both asthma and hay fever exhibited to the same atopen, one individual may

suffer from asthma only, while another has hay fever. This is also evident in the observation of L. B. Baldwin, confirmed by Aaron Brown (unpublished), that specific reagins can be demonstrated in the blood of atopic individuals before the clinical symptoms of the hypersensitiveness have appeared. To this evidence can be added the unpublished observation of Brunner and Walzer, mentioned above, that, in individuals whose blood carried antiworm reagins, asthmatic symptoms are not caused by injections of worm extracts, unless the bronchial shock organ is in the atopic state.

These observations point to the conclusion that the several atopic shock organs are in general, and also individually, subject to hereditary influence; and the evidence presented at the beginning of the present paper supports this view.

Still other evidence indicates the separate influence exerted by heredity upon the several shock organs. There is the fact that the character of the constitutional reactions produced by an overdose of an atopen differs in different individuals. There occur all combinations of asthmatic and hay fever symptoms, subcutaneous edema, and urticaria. These differences undoubtedly depend upon the degree of the atopic state of the various shock organs in the respective person.

A shock organ can be affected by the subcutaneous injection of an atopen, which, under natural conditions of exposure (contact) does not affect it. Horace S. Baldwin of the Cornell Clinic allows me to mention, in this connection, his case of eczema that was subject also to plantain pollen hay fever. On two occasions, an overdose of the pollen extract caused a decided exacerbation of the eczematous affection. The occurrence of urticaria as a result of an overdose of pollen extract injected into a hay fever subject is another instance of the same kind.

The evidence regarding the influence of heredity upon the reaction of human beings to parenteral contact with antigens may be summarized as follows:

1. Most human individuals are equally exposed to parenteral contact with foreign antigens.

2. Such contact in nonatopic persons may result in the formation of anaphylactic antibodies, but not in the establishment of atopic hypersensitiveness.

3. The reaginogenic organ in nonatopic persons has not been shown to be stimulated to reagin production by typical atopens; the reagin production observed in worm-infested, nonatopic persons seems not to be accompanied with clinical or constitutional symptoms.

Through the foregoing considerations we are led to the conclusion that an atopic individual, under adequate conditions of contact with the respective atopen, may be destined by heredity to begin to exhibit a particular clinical form of atopy (hay fever or asthma, as the case may be) at a certain age of life.

To this conclusion, however, it seems necessary to add that it is also determined in the inheritance to which particular atopen, or group of atopens, the individual is to exhibit the hypersensitiveness. There seems to be no

alternative explanation of the well-known fact that many atopic persons, exposed to the same environment, become hypersensitive to only one of the numerous atopens with which they are in contact. One of these individuals may be hypersensitive only to the grass pollens, another only to the pollen of ragweed; one only to house dust, another to cottonseed.

In the instances of successive hypersensitiveness to different atopens, the succession may, of course, be determined by inheritance.

SUMMARY

1. The several atopic shock organs are in general and also individually subject to atopic hereditary influence.

2. An atopic individual, under adequate conditions of contact with the respective atopen, may be destined by heredity to begin to exhibit a particular clinical form of atopy (hay fever or asthma) at a certain age of life to a certain atopen or group of atopens.

A COMPARATIVE STUDY OF POLLEN ANTIGENS AS DETERMINED BY THE SKIN REACTION*

By Robert F. E. Stier, M.D., and Guy L. Hollister, Spokane, Washington

GOOD results in the treatment of pollen disease are in a large measure dependent upon the accurate determination of the causative pollens by the skin tests. The choice of the method of testing, whether cutaneous or intracutaneous, depends upon the potency of the pollen antigen used. It is most important that a potent antigen be available when the cutaneous method is used, as under the most favorable conditions there is an occasional case of typical so-called seasonal hay fever who will fail to react to any pollen extract. It is our constant aim, therefore, to produce extracts that will reduce these cases to a minimum.

During the spring and summer of 1923 we were using extracts made according to Walker's method, for both testing and treating. This solution contained 14 per cent of absolute alcohol in physiologic salt solution. During that time we observed a large number of negative skin reactions in cases we felt certain should react to one of the chief pollen offenders of Eastern Washington, namely, Russian thistle. These same cases under treatment developed their usual hay fever symptoms as the height of the Russian thistle pollination season approached.

Upon investigation it was found that the Russian thistle pollen extracts, when freshly prepared, would give large skin reactions. Upon standing in the ice box for fourteen days, or seven days at room temperature, its antigenic properties had diminished to a point where negative skin reactions were obtained in individuals who had previously been proved to be highly

*Read at the Fifth Annual Meeting of the American Association for the Study of Allergy, Washington, D. C., May 16, 1927.

susceptible to Russian thistle pollen. The grass pollens remained potent a much longer time and the results with these extracts in treatment were quite satisfactory.

About the first of August, 1923, we prepared our first glycerine-sodium chloride extract and a number of cases who were obtaining poor results with the alcohol-salt extract were treated with this new extract. About 85 per cent of satisfactory results were obtained in this small series of cases for the remainder of this season, which continued for another six weeks.

As a result of this experience with the nonglycerinized solution, it was then desirable to determine what percentage of both glycerine and sodium chloride was required to produce a pollen antigen of the highest degree of potency and yet retain its keeping qualities. The solution as recommended by Clock containing 66⅔ per cent of glycerine and 33⅓ per cent of saturated solution of sodium chloride was selected as the basic solution. From this solution nine dilutions were made, the weakest one containing one part of Clock's solution and nine parts of distilled water, which gave a solution containing 6.6 per cent of glycerine and 3.3 per cent of saturated solution of sodium chloride, which represented 1.1 per cent of sodium chloride in the total volume. The amount of Clock's solution used in the intermediate solutions was progressively increased by 10 per cent in each dilution. Into these solutions was placed 1 per cent of Russian thistle pollen and extraction was carried out for a period of seven days at room temperature. For convenience we have designated these solutions as Nos. 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 as in Table I, solution No. 10 being Clock's or the basic solution and No. 1 the solution containing the smallest amount of Clock's solution.

Skin tests were made with these 10 solutions at the same time upon the same individuals who were known to be sensitive to Russian thistle pollen. The tests were repeated at six-day intervals for a period of two months. In comparing the result of these tests, it was found that solutions Nos. 5 and 6, which contained 33 per cent and 39 per cent of glycerine and 5 per cent and 6 per cent of sodium chloride respectively, gave larger reactions than the solutions with either higher or lower concentrations of glycerine and salt. At the end of the two-month period all solutions with a glycerine concentration below 40 per cent contained bacterial growth and those with 20 per cent of glycerine and less gave entirely negative skin reactions. Although solutions

TABLE I

SOLUTION	GLYCERINE PER CENT	SODIUM CHLORIDE PER CENT	REACTION AT ONE WEEK	REACTION AT TWO MONTHS	REMARKS
No. 1	6.6	1	20 mm.	0	Bacterial Growth
No. 2	12.2	2	20 mm.	0	Bacterial Growth
No. 3	20	3	20 mm.	0	Bacterial Growth
No. 4	26	4	23 mm.	15 mm.	Bacterial Growth
No. 5	33	5	25 mm.	25 mm.	Bacterial Growth
No. 6	40	6	25 mm.	25 mm.	Bacterial Growth
No. 7	46	7	23 mm.	23 mm.	Sterile
No. 8	53	8	18 mm.	18 mm.	Sterile
No. 9	59	9	15 mm.	15 mm.	Sterile
No. 10	66	11	10 mm.	10 mm.	Sterile

Nos. 5 and 6 contained a slight bacterial growth, they still gave as strong a reaction as at first. Solution No. 7 containing 46 per cent glycerine and 7 per cent of sodium chloride gave reactions almost as strong as Nos. 5 and 6 and this solution at the end of three and one-half years remains free of bacterial growth and still gives skin reactions as large as those obtained with freshly prepared extracts.

As the buffered glycerinized solutions have been recommended for extracting pollens a study was undertaken to determine the comparative skin reactions to the glycerinized sodium chloride and the glycerinized buffered solutions. As a result of the experiments just mentioned, the following solutions were prepared and are referred to by their corresponding numbers:

Solution No. 1	Saturated sodium chloride	33	per cent
	Glycerine	66	per cent
Solution No. 2	Saturated sodium chloride	33	per cent
	Glycerine	46	per cent
	Distilled water	21	per cent
Solution No. 3	Glycerine	66	per cent
	Sodium chloride	7	per cent
	Distilled water	27	per cent
Solution No. 4	Glycerine	46	per cent
	Sodium chloride	7	per cent
	Distilled water	47	per cent
Solution No. 5	Glycerine	66	per cent
	Sodium chloride	7	per cent
	Sodium bicarbonate	0.27	per cent
	Distilled water	26.73	per cent
Solution No. 6	Glycerine	46	per cent
	Sodium chloride	7	per cent
	Sodium bicarbonate	0.27	per cent
	Distilled water	46.73	per cent
Solution No. 7	Coca's solution	33	per cent
	Glycerine	66	per cent

To 100 c.c. of each of these solutions was added one gram of Russian thistle pollen, and extraction was carried out for seven days at room temperature. The solutions were then filtered through ordinary filter paper and the filtered extracts were used for making skin tests. Similar extracts were also prepared from timothy pollen. The Russian thistle and timothy pollens were chosen as they represent the most common pollen offenders in Eastern Washington. Comparative skin tests were made on 100 individuals who were known to be sensitive to the Russian thistle pollen and 50 individuals who were known to be sensitive to timothy pollen. These tests were made by applying successively, on the back of each individual, all of the above pollen solutions. Readings were made at the end of thirty minutes and measured in terms of millimeters.

RESULTS WITH EXTRACTS OF RUSSIAN THISTLE POLLEN

The original glycerine-sodium chloride mixture as recommended by Clock and designated as Solution No. 1, was used as the basic solution, from which all modifications were made. In solution No. 2, the percentage of glycerine is

decreased and the sodium chloride content is kept constant. A comparison of this solution with solution No. 1 shows that it gives 46 per cent larger skin reactions than did solution No. 1. With solution No. 3, in which the glycerine content is kept constant and the sodium chloride content is decreased to 7 per cent, there are 58 per cent of larger reactions than with solution No. 1. When both the glycerine and sodium chloride contents are decreased as in No. 4 solution, however, we find that we have 70 per cent of larger reactions than those obtained with No. 1 solution.

Thus, to briefly summarize, 46 per cent of larger skin reactions were obtained where the percentage of glycerine alone is decreased and 58 per cent of larger reactions are obtained where the sodium chloride content alone is decreased. But where both the glycerine and sodium chloride contents are decreased, the larger reactions are increased to 70 per cent.

Since the use of glycerinized buffered solutions have been recommended, we wished to determine whether the addition of sodium bicarbonate influences the extractive properties. Therefore, 0.27 per cent of sodium bicarbonate was added to solutions Nos. 3 and 4 and these solutions are designated Nos. 5 and 6. In comparing the unbuffered solution No. 3 with the buffered solution No. 5, we find that with the unbuffered solution 46 per cent of larger reactions are obtained. Further, in comparing solution No. 4, the unbuffered solution, with solution No. 6, the buffered solution, 56 per cent of larger reactions are obtained with the unbuffered solution. Apparently, then, the addition of sodium bicarbonate adds nothing to the extracting properties of the

TABLE II

REACTIONS TO EXTRACTS OF RUSSIAN THISTLE POLLEN

SOLUTION	NO. 1	NO. 2	NO. 3	NO. 4	NO. 5	NO. 6	NO. 7
	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT
Sodium Chloride	(Sat) 33	(Sat) 33	7	7	7	7	0
Glycerine	66	66	66	46	66	46	66
Sodium Bicarbonate	0	0	0	0	0.27	0.27	Coca's 33
REACTIONS							
Solution No. 1 Larger		22	20	14	26	30	22
No. 2 Larger	46		30	20	44	44	26
No. 3 Larger	58	40		28	46	50	38
No. 4 Larger	70	54	50		58	56	50
No. 5 Larger	46	36	24	24		30	34
No. 6 Larger	42	36	30	18	30		46
No. 7 Larger	58	48	38	26	40	36	
No. 1 Smaller		46	58	70	46	42	58
No. 2 Smaller	22		40	54	36	36	48
No. 3 Smaller	20	30		50	24	30	38
No. 4 Smaller	14	20	28		24	18	26
No. 5 Smaller	26	44	46	58		30	40
No. 6 Smaller	30	44	50	56	30		36
No. 7 Smaller	22	26	38	50	34	46	
No. 1 Same		32	22	16	28	28	20
No. 2 Same	32		30	26	20	20	26
No. 3 Same	22	30		22	30	20	24
No. 4 Same	16	26	22		18	26	24
No. 5 Same	28	20	30	18		40	26
No. 6 Same	28	20	20	26	40		18
No. 7 Same	20	26	24	24	26	18	

glycerine-sodium chloride mixtures, but there is a definite decrease in the extractive qualities of the glycerine-sodium chloride solutions when sodium bicarbonate is added.

A comparison with Coca's solution was also desirable to demonstrate whether the total replacement of sodium chloride by the bicarbonate solution offered any advantages. In this series it was found that 58 per cent of stronger reactions were obtained with the extract containing Coca's solution compared with the solution recommended by Clock. The solution containing 7 per cent of sodium chloride and 66 per cent glycerine (No. 3), however, gave 38 per cent of stronger reactions. The solution containing 7 per cent sodium chloride and 46 per cent glycerine gave 50 per cent of stronger reactions than the extract containing Coca's solution.

TABLE III

REACTIONS TO EXTRACTS OF TIMOTHY POLLEN

SOLUTION	NO. 1	NO. 2	NO. 3	NO. 4	NO. 5	NO. 6	NO. 7
	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT
Sodium Chloride	(Sat) 33	(Sat) 33	7	7	7	7	0
Glycerine	66	46	66	46	66	46	66
Sodium Bicarbonate	0	0	0	0	0.27	0.27	Coca's 33
REACTIONS							
Solution No. 1 Larger		36	28	8	24	12	36
No. 2 Larger	32		24	8	28	20	44
No. 3 Larger	48	48		12	36	20	44
No. 4 Larger	92	84	84		68	68	92
No. 5 Larger	48	52	48	8		28	52
No. 6 Larger	60	64	68	28	64		68
No. 7 Larger	36	32	12	4	16	4	
No. 1 Smaller		32	48	92	48	60	36
No. 2 Smaller	36		48	84	52	64	32
No. 3 Smaller	28	24		84	48	68	12
No. 4 Smaller	8	8	12		8	28	4
No. 5 Smaller	24	28	36	68		64	16
No. 6 Smaller	12	20	20	68	28		4
No. 7 Smaller	36	44	44	92	52	68	
No. 1 Same		32	24	0	28	28	28
No. 2 Same	32		28	8	20	16	24
No. 3 Same	24	28		4	16	12	44
No. 4 Same	0	8	4		24	4	4
No. 5 Same	28	20	16	24		8	32
No. 6 Same	28	16	12	4	8		28
No. 7 Same	28	24	44	4	32	28	

RESULTS WITH EXTRACTS OF TIMOTHY POLLEN

A comparison of Clock's original solution with its modifications shows but little difference between this solution and the solution in which the glycerine content alone has been diminished. When the salt content is decreased to 7 per cent and the glycerine content held constant, the larger reactions are increased to 48 per cent. When both the glycerine and salt are decreased as in solution No. 4, the larger reactions are increased to 92 per cent and in this solution we see the largest reactions when compared with all of the other solutions as indicated in Table III.

When the unbuffered solution No. 3 is compared with its buffered solution No. 5, the greater number of larger reactions are produced by the buffered solution (48 per cent) which would indicate that buffering adds to this solution. Yet the buffering of solution No. 4 adds nothing to its extracting properties, since 68 per cent of larger reactions are obtained with the unbuffered solution. When Coca's solution is substituted for the saturated sodium chloride in Clock's solution those solutions containing 7 per cent of NaCl buffered and unbuffered, give a definitely increased number of larger reactions, while in those solutions in which the NaCl content is saturated, the reactions are approximately the same.

DISCUSSION

It must be admitted that the method of comparison by means of the skin test is open to criticism but, since there is no satisfactory method known for standardizing pollen antigens, this method must be considered practical.

From the results of these comparative tests we are led to believe that an unbuffered solution having a sodium chloride content of 7 per cent and glycerine content of 46 per cent will produce an antigen that will meet the requirements of at least our section of the country more satisfactorily than any other antigen used in these experiments. In Russian thistle we have an unusually toxic pollen and because of its abundance in most parts of Eastern Washington, Eastern Oregon and Southern Idaho, a very potent extract is essential.

With the above extract we feel that this has been accomplished when the results for the past four seasons are analyzed. During this period treatment was supplied to 2,140 cases, in whom satisfactory relief was obtained in 90 per cent.

CONCLUSIONS

From this data we have concluded:

1. That the glycerinized extracts of Russian thistle are the only extracts which will retain their potency over a period of months and possibly years.

2. By reducing the sodium chloride content to 7 per cent and the glycerine content to 46 per cent, pollen extracts of Russian thistle and timothy are produced which have antigenic properties considerably higher than produced by solutions in which the concentrations of sodium chloride and glycerine are greater.

3. The addition of a buffer to this solution does not add to its extracting qualities but, on the other hand, definitely decreases the antigenic properties.

4. Satisfactory results in treatment are obtained with extracts containing 7 per cent of sodium chloride and 46 per cent of glycerine.

REFERENCES

[1]Clock, R. O.: A Stable Pollen Antigen, Jour. Infect. Dis., 1917, xxi, 523.

[2]Coca, A. F., and Milford, E. L.: Studies in Specific Hypersensitiveness: XVII. The Preparation of the Fluid Extracts and Solutions for Use in Diagnosing and Treating Atopic Conditions, Jour. Immunol., 1925, x, No. 2, p. 555.

EOSINOPHILIA IN ASTHMA, HAY FEVER, AND ALLIED CONDITIONS*

By Grafton Tyler Brown, B.S., M.D., F.A.C.P., Washington, D. C.

GENERAL CONSIDERATIONS

Eosinophiles are white blood corpuscles of the polymorphonuclear variety, averaging in size from 10 to 14 microns, with definite but pale-staining nuclei. Their distinguishing characteristics are the large, coarse, highly refractive granules within the cytoplasm which exhibit special affinity for eosin and other acid dyes. Eosinophiles are quite susceptible to rupture and they frequently are seen in smears as a mass of reddish granules, among which may be found a palely-staining lobulated nucleus.

These cells are developed directly from the large eosinophilic myelocytes found commonly in the bone marrow and, to some extent, in the spleen. Eosinophilic myelocytes vary considerably in size, even under normal conditions, being anywhere from one-half to twice as large as the eosinophilic leucocytes. They have rounded nuclei, somewhat more heavily staining than the nuclei of the eosinophilic leucocytes, and the granules, many times, are not so even and regular as seen in the peripheral blood. The myelocytes appear to be indirectly developed from the myeloblasts, going through a transition of the so-called premyelocytes, in which stage they accumulate their granules and show beginning differentiation into the various varieties of neutrophilic, basophilic, and eosinophilic staining affinity.

Under normal conditions the number of eosinophiles found per cubic millimeter of blood ranges from 50 to 400, the normal eosinophilic percentage being about 1 to 4 per cent of all the leucocytes. Usually any increase above 4 per cent up to 10 per cent is considered a moderate eosinophilia; from 10 to 20 per cent, marked eosinophilia; and above 20 per cent, excessive eosinophilia.

The greatest absolute increase in eosinophiles is seen in the early stages of myelogenous leucemia, in which a great variety of different forms may be demonstrated, not only of the eosinophilic polymorphonuclears themselves, but all varieties of eosinophilic myelocytes. While the total number is increased, the percentage is many times not markedly altered, owing to the increase of all the white blood corpuscles of the myelogenic type.

Certain cases of bronchial asthma probably give the largest percentages of eosinophiles noted. Dr. Hunter reported one case to me, in which the eosinophile count was 87 per cent. The eosinophilia in bronchial asthma is by no means a constant finding. In parasitic infections, particularly the nematodes, eosinophilia is usually a constant finding. This does not hold true, however, of many of the protozoa and some of the cestodes. Eosinophiles in

*Read at the Fifth Annual Meeting of the American Association for the Study of Allergy, Washington, D. C., May 16, 1927.

nematode infections usually range between 10 and 20 per cent, being probably highest in hookworm and trichinella infestations.

Eosinophilia is also frequently observed in scarlet fever, which is one of the clinical laboratory aids in differentiating this disease from measles. Eosinophiles are found in increased numbers in the blood in certain skin diseases, particularly pemphigus, prurigo, psoriasis, and urticaria. The presence of eosinophilia seems to depend upon the cause or the nature of the skin disease rather than upon the condition of the skin per se. We also occasionally meet with eosinophilia in subacute and chronic tuberculous conditions, and sometimes in chronic streptococcus infections, and in certain anaphylactic states. Occasionally an increase in eosinophiles is noted in Hodgkin's disease.

Tissue eosinophilia, with or without the occurrence of any material increase of the eosinophiles in the blood stream, is seen in many cases of chronic lymphadenitis, chronic appendicitis, and in a variety of conditions presenting the histologic picture of chronic granulomatosis. Eosinophilia in the blood is also met with in a number of other conditions, in which exhaustive clinical, laboratory, and even autopsy studies fail to reveal the reason for the eosinophilic increase, and for the want of a better understanding, must be termed idiopathic.

The eosinophiles appear to be stimulated in their production by certain substances elaborated by a number of parasites, particularly of the intestinal variety, and by certain tissue changes seen in bronchial asthma, asthmatic bronchitis and other infectious conditions of purely bacterial origin. The eosinophiles appear to be stimulated in their production and attracted to certain tissues of the body in a manner similar to that in which the polymorphonuclear neutrophiles are influenced, namely, positive chemotaxis. In the instance of the eosinophiles, however, this stimulation and positive chemotaxis seems to be exerted upon the eosinophilic myelocytes and leucocytes rather than upon the neutrophilic type. The exact nature of this virus or chemotactic influence is not known. Chemical changes in the blood and, so far as can be determined, microchemical changes in the tissues are not of sufficient definiteness to explain the phenomenon.

EOSINOPHILIA IN ALLERGY

In an effort to determine the significance of eosinophilia in allergy, a painstaking analysis was made of 370 consecutive differential leucocyte counts on 346 different patients with asthma, hay fever, or some allied condition.

It is rather generally believed that eosinophilia in asthma or hay fever patients is practically diagnostic of protein sensitization. I am forced to disagree with this opinion, however, as I have seen definitely sensitive asthma or hay fever patients who had no eosinophilia, either during or between attacks. Furthermore, some of the highest eosinophile percentages I have encountered have been in nonsensitive or bacterial cases. There were only four patients in this series with excessive eosinophilia (above 20 per cent), namely, one perennial hay fever patient and three asthmatics, and all four of them were nonsensitive.

In most every patient in this series with marked or excessive eosinophilia, the stools were carefully examined for the presence of parasites or ova, but none were found to account for the eosinophilia.

Sex.—There were 159 males and 211 females in this series. The average percentage of eosinophiles for the males was about 6 per cent, and for the females was about 5½ per cent. Sex, therefore, has probably no influence on blood eosinophilia in allergy.

Age.—The average age of all the patients with blood eosinophilia was about thirty-seven years, whereas the average age of all the patients whose blood eosinophiles were within normal limits was about thirty-nine years. From this it may be inferred that, on an average, blood eosinophilia is encountered in slightly younger individuals than is a normal percentage of eosinophiles. There was in this series, however, one patient sixty-nine years of age whose eosinophiles were 18 per cent, and another patient sixty-four years old whose eosinophiles were 22 per cent.

Asthma.—By means of skin tests, asthma patients are divided into two groups: first, those who are found sensitive to some foreign protein (food, animal epidermal, pollen, or miscellaneous inhalant), designated as true bronchial or allergic asthma; second, those who are not found sensitive to any foreign protein, designated as asthmatic bronchitis or bacterial asthma. In this series, there were 193 differential leucocyte counts on patients with asthma. The eosinophile average for all the sensitive asthma patients was about 7 per cent, and for the nonsensitive asthmatics was also about 7 per cent. Sensitization in asthma, therefore, has no influence on blood eosinophilia.

Bronchitis (Nonasthmatic).—In contrast with asthmatic bronchitis, there were 12 cases of nonasthmatic bronchitis in this series, with an eosinophile average of only about 2 per cent. In other words, asthmatic bronchitis produces a much higher eosinophile average than does nonasthmatic bronchitis.

Hay Fever.—There were 90 differentials on hay fever patients (35 seasonal and 55 perennial), with an eosinophile average of about 6 per cent. The average percentage of eosinophiles for seasonal hay fever was about 5½ per cent; and for perennial hay fever was about 7 per cent, being almost exactly the same in the nonsensitive as in the sensitive patients. In hay fever, therefore, just as in asthma, sensitization has no influence on eosinophilia.

"Colds."—There were in this series 12 cases of frequent "head colds," three of them complicated by sinus trouble. The eosinophile average for this group was only about 3 per cent. It would seem from this that recurrent "head colds," with or without sinus trouble, do not produce as high an eosinophile average as does hay fever.

Eczema.—There were 46 differentials on patients with eczema in this series, with an eosinophile average of exactly 5 per cent. The eosinophile average for the nonsensitive eczemas was about 4½ per cent, whereas for the sensitive eczemas it was about 6½ per cent. Although it is based on relatively few eczema cases, it may be inferred that protein sensitive eczema produces a higher blood eosinophile average than does nonsensitive eczema.

Urticaria.—Eleven differentials on patients with urticaria in this series gave an eosinophile average of about 4 per cent. It is evident from these few cases that urticaria does not always produce a definite blood eosinophilia.

Duration of Disease.—The average duration of disease of all the patients with blood eosinophilia was about eleven years, whereas the average duration of disease of all the patients whose blood eosinophiles were within normal limits was about thirteen years. From this it may be inferred that, on an average, the longer the duration of disease, the less likely for blood eosinophilia to be encountered. There was in this series, however, one patient with 22 per cent eosinophiles, who had been having asthma for fifty-two years.

Sensitive or Nonsensitive.—For the entire series, the eosinophile average of the nonsensitive cases was about 5½ per cent and of the protein sensitive cases was about 6 per cent. It has been previously stated that in asthma and hay fever, protein sensitization has no influence on blood eosinophilia.

Type of Sensitization.—In this series, the eosinophile average for the food sensitive patients was about 7 per cent, for the animal epidermal sensitive patients exactly 6½ per cent, and for the pollen sensitive ones about 6½ per cent. Apparently there is no connection between the type of sensitization and the percentage of eosinophiles in the blood.

Sputum.—Direct smears from the sputum of 123 patients with asthma or bronchitis in this series, were examined microscopically for the presence of eosinophiles. They were divided into four groups according to the number of eosinophiles present, namely: none, few, moderate number, and large number. In comparing the number of eosinophiles in the sputum with the percentage in the blood it was found that: in the group with none in the sputum, the blood eosinophile average was about 5½ per cent; in the group with a few eosinophiles in the sputum, the blood average was about 6½ per cent; in the group with a moderate number in the sputum, the blood average was about 8 per cent; and in the group with a large number in the sputum, the blood average was about 9 per cent. In other words, the number of eosinophiles in the sputum of patients with asthma or bronchitis runs directly parallel with the percentage of eosinophiles in the blood.

Blood Calcium.—It has been shown in a previous paper[1] that no relation exists between the percentage of eosinophiles in the blood and the calcium content.

All the differential leucocyte counts and stool examinations referred to in this paper were performed by Dr. Oscar B. Hunter, professor of bacteriology and pathology, George Washington University Medical School.

REFERENCE

[1]Brown, G. T., and Hunter, O. B.: Calcium Deficiency in Asthma, Hay Fever and Allied Conditions, Ann. Clin. Med., Oct., 1925, iv, 299.

THE INFLUENCE OF THE CAPILLARY CIRCULATION UPON CERTAIN ALLERGIC CONDITIONS*

By Edward Scott O'Keefe, M.D., Boston, Mass.

THERE is a definite and important relation between the capillary circulation and allergic conditions. Variations in capillary permeability affect the amount and rate of protein absorption from the intestinal tract and later influence the amount of foreign protein which comes into contact with the tissues supplied by the capillary network. The same factors which influence the capillary circulation have long been known to be aggravating factors in allergic diseases.

Within the last few years work by Krogh[1] and later by T. Lewis[2] have thrown new light upon the functions and structure of the capillaries. The capillaries are no longer considered to be endothelial tubules reacting passively to changes in the heart and great vessels. The Rouget cells have been demonstrated as isolated cells scattered upon the walls of the capillaries. Each cell consists of a mass of nucleated protoplasm with branched processes which encircle the capillary. Upon these cells the capillaries depend for their ability to contract and relax under the influence of certain stimuli.

Both Krogh and Lewis agree that the permeability of the capillaries is increased by a variety of stimuli, mechanical, thermal, chemical and photogenic. Lewis is satisfied to say that the increased permeability arises from these stimuli. He feels that the exact mechanism is unknown. Krogh goes further and states, after a variety of ingenious experiments, that the increased permeability arises from, and is directly due to the dilatation of the capillaries. He feels that there is an actual increase in the size of the interstices of the capillary wall during dilatation, which permits, at that time, the passage of even large molecules, such as the protein molecules, into the surrounding tissues.

The conception that increased capillary permeability and capillary dilatation go hand in hand is of great importance in any consideration of allergic conditions. It is significant that the four classes of physical agents mentioned above as stimuli producing capillary dilatation have long been recognized as having an unfavorable influence on eczema. In fact the entire dermatologic program for this disease is, in its final analysis, an effort to protect the skin from the reactions following exposure to these agents.

Not only the cutaneous capillaries but those of the intestinal tract play a part in eczema. Faulty digestion resulting in irritating intestinal contents might be expected to cause a change in the permeability of the capillaries of the villi of the small intestine. In this connection, the work of Schloss[3] and

*Read before the American Association for the Study of Allergy at Washington, D. C., May 16, 1927.

Anderson in 1923 is of especial interest. Working upon infants suffering from diarrhea they found, in a considerable number of cases, evidence that the normal protection of the organism from foreign protein was lacking. They demonstrated by precipitin and allergic tests that it is not infrequent, during intestinal disorders, for milk protein to pass intact through the intestinal wall into the blood and body fluids. Such a finding would not be unexpected in light of Krogh's researches. It is also in accordance with clinical observations upon the rôle of fat and carbohydrate indigestions both of which are recognized as predisposing causes of infantile eczema.

The relation between allergy and the physical agents heat, cold, light and mechanical stimulation receives mention from Duke[4] in his excellent book upon allergic conditions. The phenomena following these stimuli Duke has classified, as a separate group, under the heading Physical Allergy. He considers these phenomena to be due to a specific hypersensitiveness to the action of physical agents and is inclined toward the view that a foreign protein is formed in the body as a result of these physical stimuli. To this foreign protein the individual has become sensitized. The repetition of the mechanical stimulus is considered to produce such a hypothetic protein and to produce the manifestations which are classed under the heading of physical allergy.

The physical agents to which Duke refers have been shown by Krogh to be definite capillary stimuli. In normal individuals he has shown that a capillary dilatation results from such stimuli and that increased capillary permeability follows with local exudation of serum. Such serum was analyzed by Tork and Vas[5] and found to have a 3 per cent protein content—evidence that a marked capillary permeability exists.

The response to physical agents in the group cited by Duke is similar to the response occurring in normal individuals and to a more marked extent in urticaria factitia. In the three groups there is an exudation of serum from the cutaneous capillaries. At this point the similarity ends. Duke's cases show, in addition to the normal capillary permeability, a response similar to that occurring in allergic diseases. The explanation of this seems to lie in the fact that the serum of Duke's patients contains foreign protein which produces a characteristic allergic reaction when released from the capillaries.

In some of his cases which showed abnormal response to light Duke has noted a certain amount of immunity following repeated exposures to the sun or to the violet end of the spectrum. He interprets this as a filtering out of the violet rays by the tanning of the skin which normally occurs. This immunity seems, however, to be a normal capillary response to such repeated stimuli rather than any protective action of the skin pigment. This has been demonstrated by C. With[6] who obtained a similar amount of immunity to light in vitiliginous areas of skin in which of course pigmentation could be excluded as a factor.

The peculiarity of the group included under the term physical allergy seems to lie in their capillary response rather than in any unusual allergic response. Just as we find a distinct group of individuals, with the condition known as urticaria factitia, having capillaries which show a distinctive response to mechanical stimuli so there seems to be other groups showing a dis-

tinctive capillary response to light, heat or cold. When such individuals are in the allergic state manifestations such as Duke describes under the heading of physical allergy may follow upon the application of the proper physical stimuli. This group will, I am sure, upon further investigation, be found to be sensitized to some of the common forms of protein. Their peculiarity lies only in their excessive response to capillary stimulation.

Finally, aside from the ordinary stimuli which may affect the capillaries, there is evidence that protein sensitization of itself results in an increased capillary permeability as shown by Manwaring's[7] experimental work upon the lungs of sensitized dogs.

A consideration of the possible influence of capillary permeability upon allergic conditions forces upon us the great significance of Manwaring's view when he says, "Capillary permeability will ultimately be shown to be the dominant fundamental physiologic change in protein sensitization to which all other anaphylactic reactions are secondary."

REFERENCES

[1]A. Krogh: Anat. and Physiol. of Capillaries, 1924.
[2]T. Lewis: Heart, 1924, xi.
[3]Schloss and Anderson: Am. Jour. Dis. Child., Nov., 1923, xxvi, 45.
[4]W. W. Duke: Asthma, Hay Fever, Urticaria and Allied Manifestations of Allergy, 1925.
[5]Tork and Vas: Quoted in Krogh's Anat. and Physiol. of Capillaries, 1924.
[6]C. With: Brit. Jour. Dermat., May, 1920, xxxii, 145.
[7]Manwaring et al: Jour. Am. Med. Assn., February, 1924, lxxxii, 542.

FACTORS WHICH DETERMINE THE POLLEN CONTENT OF THE AIR*

By Ray M. Balyeat, M.A., M.D., Oklahoma City, Okla.

THE most important wind-borne pollinated plants in the territory surrounding the principal centers of the United States have been carefully investigated by men who are interested in asthma and hay fever. It has been noted that many factors play a part in determining the pollen content of the air, and varied evaluations have been placed upon them. I wish to discuss these different factors and compare the relative pollen content of the air as found in three large cities in different sections of the United States.

METHODS OF STUDY

Daily, from March 27, 1926, to November 10 of the same year, my botanist, Professor T. R. Stemen, and I studied the pollen content of the air in Oklahoma City. During this same time a Government meterologic report was carefully watched. The botanist exposed oil-coated slides in various sections of the city, from which he made microscopic examinations and differential pollen counts. It was not necessary to stain the slides in order to differentiate

*Read at the Fifth Annual Meeting of the American Society for the Study of Allergy, Washington, D. C., May 16, 1927.

pollens of one botanical group from those of another. We found some difference in the pollen from different species of plants in the same botanical group, but the difference was not great enough to distinguish them always definitely.

The method of counting was as follows:

A 10 X eye piece was used and the barrel was pulled up as high as possible. The low power was used, and ten trips across the slide were made, counting all that fell in the field of vision.

The above method was one agreed upon by O. C. Durham, who was making similar studies in Kansas City and Chicago. We felt that in order to compare our findings it would be necessary for us both to use the same standard in counting.

EFFECT OF PRECIPITATION

The amount of precipitation plays a very definite part in several ways in determining the amount of pollen that actually remains in the air. In the first place, the amount and the distribution of rainfall during the growth of the plants determine largely the number of the plants and the extent of their growth. They also determine the amount of pollen that will be produced by the plant life, inasmuch as large stalks of Bermuda or ragweeds will produce more pollen than small ones. After the plants have matured and are pollinating, the amount of rainfall and the period over which precipitation takes place are usually definite factors in regulating the pollen content of the air. This is not always the case, however. For example, from nine o'clock P.M. on the second day of September until three o'clock A.M. on the third of September, the precipitation in Oklahoma City amounted to 3.16 inches, but on September 3 the relative pollen count was 6800, being next to the highest peak during the entire season. On the day following the heavy precipitation first mentioned, the wind began to blow about three o'clock in the morning and continued throughout the day. The percentage of sunshine on the following day was 100. Under such conditions the precipitation had practically nothing to do with regulating the amount of pollen that was found in the air. Of course, during the time of precipitation, the pollen was practically all washed out of the air, but with high wind and sunshine, the air was soon saturated again. A slow rain over a period of two or three days accompanied by cloudy weather, however, will practically free the air entirely of pollen.

During the months of August and September, 1926, the amount of rainfall in Oklahoma City, according to Government records, was 8.76 inches. This was more than the average rainfall for that time of the year; but, as can be seen by the chart, more than 50 per cent of it fell on only two different days, so it interfered but little with the pollen that had been liberated into the air.

WIND AS A FACTOR

The velocity of the wind determines, to a considerable extent, the amount of pollen that gets into the air, how far it will be carried, and the amount that comes in contact with the nasal mucous membrane of the hay fever sufferer. The time of the day in which the wind blows is important. For exam-

ple, if there is a stiff gale throughout the early morning hours, during which time the pollination is the heaviest, it would carry more pollen into the air than a similar gale during the evening. The lowest wind velocity over a period extending from August 11 to October 1, for any one day, in Oklahoma City, was six miles, and the highest velocity was 17.2 miles. The average wind velocity over the period mentioned was 9.9 miles.

From a clinical standpoint, the wind is a very definite factor in the cause of hay fever symptoms, for on windy days patients will complain more bitterly. Our pollen counts show that when all other factors are equal, the number of pollens on the plates is almost in direct ratio to the wind velocity. It ought to be this way. For example, if the wind is blowing at five miles an

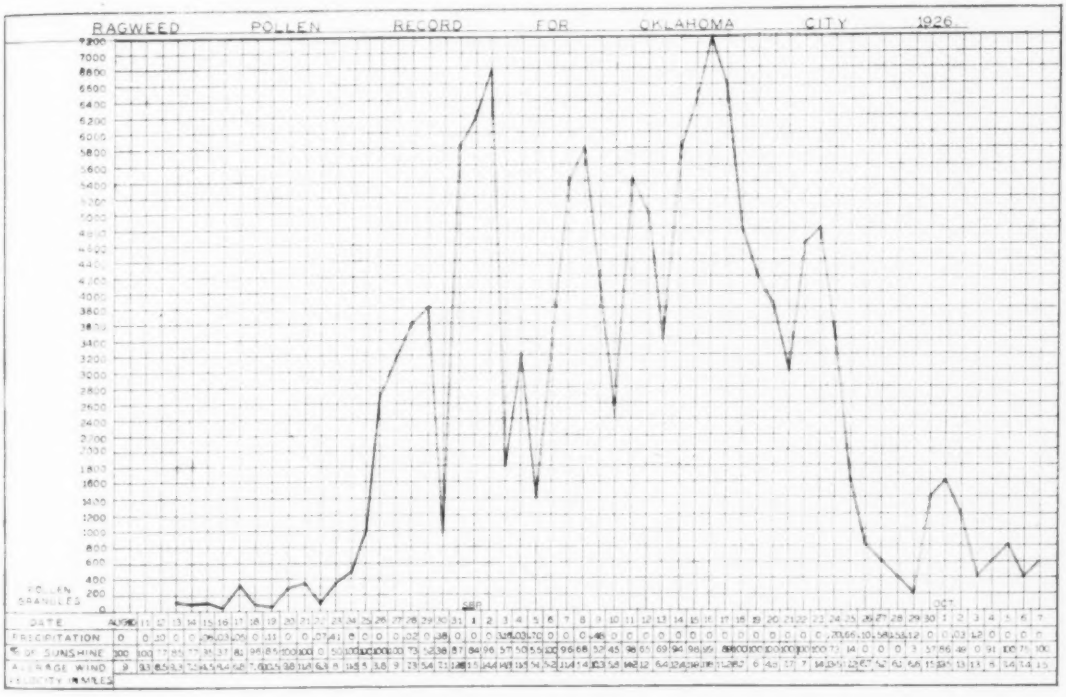


Chart I.—A study of the effects of precipitation, sunshine and wind velocity on the pollen content of the air.

hour, let us assume five pollen granules would come in contact with the pollen plate or the mucous membrane. If the wind were blowing at fifteen miles an hour, there should come in contact with our pollen plates and with the mucous membrane of the hay fever sufferer, three times five pollen granules, or fifteen pollen granules, over the same surface, naturally would produce much more severe ones.

THE PART PLAYED BY SUNSHINE

Every botanist who has collected pollen has noticed the poor production of pollen on cloudy days. In fact one may fill the pollen house with pollinating plants and find practically no pollen at all on the folowing morning if it

is cloudy, while if the sun shines, the production will be very great. From Chart I the effect of sunshine can be readily seen. Over the period in which the percentage of sunshine is 100 or nearing 100, even if the rainfall is fairly great, the pollen content is high; but if the rainfall is zero and the percentage of sunshine is low, the pollen count is relatively low. The figures relative to sunshine shown in the chart are the percentages of possible sunshine during the day. During the period from August 11 to October 1 there were twelve days with 100 per cent sunshine, and eleven other days with more than 85 per cent sunshine. From a clinical standpoint, one soon learns that sunshine plays a very definite part in determining the amount of pollen that gets into

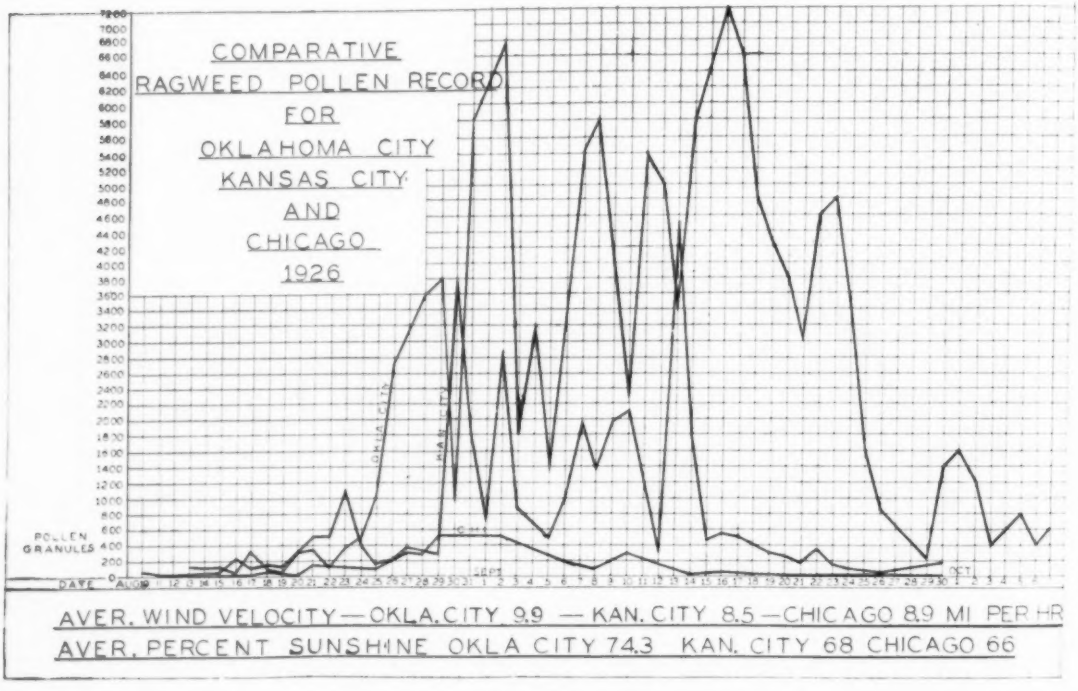


Chart II.—A study of the factors which might make a difference in the pollen content of the air in three large cities.

the air, and from our study of plant life we learn that the amount of sunshine determines very largely the amount of pollen that is actually liberated from the pollen pods.

IMPORTANCE OF PLANT LIFE

The greatest factor in determining the amount of pollen that can be found in the air is that of the abundance of plant life. If the plant life is scarce, it makes no difference whether the sunshine is 100 per cent, the wind velocity great, or the rainfall light, for it would be impossible for much pollen to be found in the air. The actual location of the majority of plants is not such an important factor if they are within range of three or four miles of a city, for from this distance the pollen will be brought in by means of the

wind. This will hold true for all plants with the exception of a few whose pollen is very heavy. We found it made very little difference where our plates were located as to the relative pollen count.

COMPARATIVE POLLEN RECORD FOR OKLAHOMA CITY, KANSAS CITY AND CHICAGO

During the late summer and fall of 1926 we made daily ragweed pollen counts, which are shown in curve of Chart II. Similar work was done in Kansas City, as is shown in the same chart; likewise the record of a pollen curve for Chicago in 1925 is shown. In observing the three curves, one can readily see a vast difference between the pollen content of the air in Chicago and in Kansas City, or between Chicago and Oklahoma City. The difference between the Kansas City and Oklahoma City curves is not quite so striking.

You will note that the highest pollen content of the air in Chicago for 1925 was 480 pollen granules, for Kansas City in 1926 was 4800 granules, and for Oklahoma City 7200 pollen granules. It is also of interest to note that the dates on which the first pollen granules were found in all three cities were practically the same—Aug. 12 and 13—and that the first peak for all three cities was on Aug. 29 and 30. One will notice from the Chicago curve that, from Sept. 14 and on, the curve hugs the base line, and that the Kansas City curve drops to a low ebb about that time and continues with a small amount of pollen from then on. The Oklahoma City curve does not drop until Sept. 25.

The question naturally arises as to why the pollen content of the air is so light in Chicago as compared with Oklahoma City and Kansas City. Is it the difference in the wind velocity, the sunshine, or precipitation between these three cities, or is there some other factor? If you will note from the chart, the average wind velocity over the period studied in Oklahoma City was 9.9 miles, Kansas City 8.5 miles, and Chicago 8.9 miles. You will readily see that the difference is very little. Therefore, the difference in wind velocity could not be the main factor. The average per cent of sunshine in Oklahoma City was 74.3, in Kansas City 68, and in Chicago 66. Although there is some difference in the per cent of sunshine in the three cities, it does not seem reasonable to believe that the per cent of sunshine could possibly make the difference in the pollen content of the air.

The rainfall in Chicago in 1925 is not shown on this curve but from the meterologic reports it was not as great as that of Oklahoma City in 1926. So the difference in rainfall of the three cities could not make the difference between the amount of pollen that is actually found in the air. Therefore the factor which has made such a wide range of difference in these three pollen curves must be one other than rainfall, percentage of sunshine, or wind velocity. In my judgment there is only one other factor that it could possibly be, and that is the difference in the amount of plant life near these three large centers.

If you will travel from Oklahoma City to Chicago during August and September, you will find that the ragweed growth, like the growth of other plants around Oklahoma City, is greater than that of the same plants around Kansas City. The difference is great enough so that it is fairly easily de-

tected. As one goes to Chicago, further on he can see a striking difference between the plant life around Oklahoma City and Chicago. When one takes into consideration the fact that at least 50 per cent of the time the wind is blowing off the Lakes, thereby coming off a territory in which there are no plants, it seems reasonable to believe that the amount of pollen in the air in Chicago should be at least 50 per cent less than the pollen in the air in Oklahoma City, even if the plant life on the other side of that city were equal to that of Oklahoma City. Although the Lakes reduce the amount of plant life that might produce pollen very largely, the pollen content in Chicago is so much less than that in Kansas City and in Oklahoma City, that even taking the Lakes into consideration, it could not reduce the content to such a low ebb unless there were another factor; and that other factor, I am sure, is that of the difference in the abundance of wind-borne pollinated plants around the three centers mentioned.

THE ORAL ADMINISTRATION OF POLLEN*

By J. H. Black, M.D., Dallas, Texas

THE first definite attempt to immunize pollen-sensitive individuals to their specific pollens was that of Dunbar[1] who, working on the hypothesis that the active substance of pollen was a toxin, injected animals with pollen and used the antiserum thus obtained in an effort to secure a passive immunity in his patients. In 1911 Noon[2] and Freeman,[3] with the same belief regarding the active substance, gave a series of injections of pollen extracts to their patients with the hope of producing an active immunity and protection against clinical hay fever.

While our present form of treatment dates from the work just mentioned and that of American workers who quickly followed them, our opinions as to the active substance of pollen and our ideas as to the mechanism by which relief is obtained have undergone radical revision. Sufficient data are not available to permit definite conclusions about either but one may be permitted to say, first, that evidence is accumulating which tends to confirm the belief that the active constituent of pollen probably is not protein; second, that no one believes that pollen therapy brings about a true immunity; third, that recent evidence discredits the idea that treatment is specific desensitization;[4] and, fourth, that no evidence exists for the assumption that a tolerance is induced. The finding of a specific "reagin"[5] in the blood of pollen-sensitive individuals brought some hope that it might explain the situation but the demonstration[6] that reagin does not in any detectable manner alter the activity of the "atopen," leaves the question unanswered.

Since it has been assumed that the atopen in pollen is protein or indissol-

*Read at the Fifth Annual Meeting of the American Association for the Study of Allergy, Washington, D. C., May 16, 1927.

ubly associated with it, hypodermic administration has seemed the only rational means of treatment. If this assumption is not correct, the necessity for this method no longer exists and other avenues of approach may be considered. There are at least three objectionable features of hypodermic therapy. First, there is always a certain amount of pain which becomes a matter of consequence with children and those to whom concentrated glycerine-saline extracts are given. Second, patients who have no physician accessible must resort to self-medication or be denied treatment. Third, and by far the most important, constitutional reactions occur not infrequently in spite of all precautions.

In order to determine if protection could be secured by the oral administration of pollen, and also to learn something of the absorption, distribution and elimination of pollen thus administered, giant ragweed pollen—to which I am sensitive—was taken orally by me. This is a brief preliminary report upon this work.

The extract used was a 5 per cent glycerine-Coca solution of giant ragweed made by standing twenty-four hours at room temperature and filtered through paper. One-tenth c.c. of this extract diluted 1-10,000 was the minimal amount required to produce a mild hay fever within two minutes after being instilled into my nostril. A dilution of 1-100,000 injected intradermally into my forearm produced a typical wheal with pseudopods.

The initial dose was 0.1 c.c. of the 5 per cent extract diluted with approximately 200 c.c. of water and taken on an empty stomach with the belief that it would be passed rapidly into the intestine without stimulating gastric secretion. The dose was increased by doubling until 1.0 c.c. was reached, after which 0.1 c.c. increments were used. Doses were taken three times daily. The maximum dose was 2.5 c.c., which gave a total of 7.5 c.c. in the twenty-four hours. This is fifteen times the final dosage usually required hypodermically in our locality and which has protected me during the past three ragweed seasons. The total amount taken was 34.5 c.c. in seven days' time.

Since this was done outside the ragweed season, an attempt was made to measure the degree of protection secured by the lowering of the sensitiveness of the nasal mucosa to instillation of ragweed pollen into the nostril. Blood was drawn from a vein each day, the serum separated and used for intradermal injection to determine the presence of ragweed atopen. Urine was collected, filtered through a Berkefeld filter and tested intradermally to determine if elimination occurred in this way. Feces were extracted with distilled water and put through a Berkefeld candle, then used intradermally to learn if some of the material was coming through unabsorbed.

The first statement which can be made regarding our findings is that the quantities of pollen used produced no unpleasant symptoms of any kind. There is little taste to the well-diluted extract and nausea or pain was not experienced. No constitutional reaction occurred, which is in marked contrast to my experience in taking hypodermic therapy.

Whereas, before this treatment, 0.1 c.c. of a 1-10,000 dilution of this extract produced sneezing in two minutes when instilled into my nostril (and reaction to this minimal amount is a constant), on the day following cessation

of treatment 0.1 c.c. of a 1-1250 dilution, or eight times the usual amount, was required. Whether this is an entirely reliable index of protection I do not know. It certainly imitates, as near as may be, the natural mode of attack.

Levine and Coca[7] have injected pollen intravenously in normal individuals and found it in the blood up to the seventh day and demonstrated it in the urine during the first forty-eight hours. Two sensitive individuals who had received pollen treatment over a period of eight weeks showed none in their blood.

My blood was drawn on the last two days of treatment, and one day, five and seven days respectively after treatment was discontinued. The serum was separated and injected intradermally into my forearm, into passively sensitized areas in a normal skin, and into a nonsensitive skin.

In my skin the reactions obtained during the last two days of treatment equalled in size those resulting from the injection of a 1-20,000 extract. One day after treatment was stopped the wheal was slightly more than one-half as large, while on the fifth and seventh days after treatment the reaction was not appreciably larger than the control. Injections of serum into a nonsensitive skin were made at the same time as the above and were uniformly negative. In sensitized areas in a normal skin reactions paralleled closely those in my own arm. Evidently the atopic substance was being absorbed in appreciable quantities and was unchanged by contact with reagin. Elimination from the blood was rapid.

Since it has been shown that reagin is neutralized in the skin and in vitro by contact with its specific atopen,[6] it is interesting to note that, in this instance, atopen and reagin apparently existed coincidentally and could be demonstrated in the serum at the same time. One-tenth c.c. of my serum drawn on each of the last two days of treatment was injected intradermally into a normal individual. On the following day a 1-100 dilution of pollen was injected into these sites. Typical reactions were obtained which were only slightly smaller than those resulting in sites sensitized by my serum drawn prior to treatment. It would seem that, while the atopen was present in the serum, in demonstrable amount, it was not sufficient to neutralize all the reagin, at least.

The filtered urine was tested during the last three days of treatment. The size of the wheal in sensitized skin increased progressively paralleling the increase in amount of pollen ingested, while in normal skin reactions did not occur. Urine passed on the seventh day after treatment gave a small, but definite, reaction.

A watery extract made of feces passed on the last two days of treatment produced large wheals in sensitized skin and no reaction in the normal.

SUMMARY

1. The oral administration of large doses of pollen extract to a sensitive individual is apparently devoid of danger and causes no unpleasant symptoms. It is probable that the slow absorption by this route makes it possible to administer large amounts without danger of constitutional reactions.

2. That an appreciable amount of the pollen is absorbed is shown by its presence in the circulating blood and its elimination in the urine. That some of it is not absorbed is shown by its presence in the feces.

3. A certain amount of protection may be assumed by the lowered sensitivity of the nasal mucosa. Clinical protection could not be proved in this work because it was done outside the pollen season.

4. The coexistence of atopen and reagin in the circulating blood is shown.

CONCLUSION

While this fragmentary report is not offered as final evidence, it would seem justifiable to conclude that the oral administration of pollen extract offers a satisfactory means of securing protection against pollen and is free of the objectionable features of hypodermic therapy.

NOTE.—Since the above was written approximately one hundred fifty cases of pollen asthma and hay fever have been treated with this method with most gratifying results. A detailed report is in preparation.

REFERENCES

[1]Dunbar: München, 1903.
[2]Noon, L.: Lancet, 1911, i, 1572.
[3]Freeman, J.: Lancet, 1911, ii, 814; 1914, i, 1178.
[4]Levine, Philip and Coca, Arthur F.: Jour. Immunol., 1926, ii, 449.
[5]Prausnitz and Küstner, H.: Centralbl. f. Bakt., Orig., 1921, lxxxvi, 160.
[6]Coca, A. F., and Grove, E. F.: Jour. Immunol., 1925, x, 445.
Levine, Philip, and Coca, Arthur F.: Jour. Immunol., 1926, ii, 411.
[7]Levine, Philip, and Coca, Arthur F.: Jour. Immunol., 1926, ii, 449.

CLINICAL INVESTIGATIONS IN ALLERGY

A REVIEW OF 189 PATIENTS OF ASTHMA AND HAY FEVER CLINIC*

BY LEON UNGER, M.D.,† CHICAGO

IN MAY, 1924, a clinic for the care of patients suffering from the so-called allergic diseases was opened at Northwestern University Medical school. At first there were but few patients but the number has increased steadily to the present time.

This group under study consists chiefly of cases of bronchial asthma and hay fever; besides these there are a few cases of allergic rhinitis, urticaria and angioneurotic edema. Other diseases such as eczema and epilepsy have for some years been thought by some to have a relation to allergy, but the connection is not as well established as in those just referred to.

One hundred and eighty-nine patients comprise this study. There are numerous others who were examined in the clinic and immediately referred to some other department or who came only once or twice to the clinic.

*Read before the American Association for the Study of Allergy, Washington, D. C., May 16, 1927.
†Assistant Professor, Department of Medicine, Northwestern University Medical School.

These are not counted in the above number. Of these cases 135 are white and 54 colored; 96 males and 93 females. The average age is 32. The average duration of symptoms is six years. There is a family history of asthma or hay fever in 36 of the cases or 19 per cent.

Complete histories and physical examinations were done in all of the cases. In addition all had Wassermann, urine and blood count tests done; a large majority also had sputum and chest x-ray examinations. Most of the patients were also carefully examined in the nose and throat dispensary and where indicated x-rays of the sinuses were carried out. Every effort was made toward correct diagnoses.

Bronchial asthma was diagnosed in 121 of the 189 cases. This diagnosis was based chiefly on the history of the attacks of dyspnea, cough and wheezing starting usually in children or young adults. Physical examinations varied, wheezing sounds and the typical musical chest findings were present during an attack and often between attacks; but frequently there were no râles between spells.

Skin tests were done more or less completely on 88 of these 121 cases. Thoroughness was our slogan and we tested out the patients as completely as possible. Most of these patients had from 100 to 200 different cutaneous tests performed; in addition some intracutaneous experiments were carried out. In the other 33 cases tests were either not done at all or were incomplete.

Of the 88 patients suffering from bronchial asthma who were thoroughly skin tested 74 or 85 per cent gave positive findings, 13 or 15 per cent were completely negative; 21 of the positives were found in patients who had seasonal asthma and hay fever and who only developed asthma during the pollenating season of the weeds to which they were sensitive. All these gave positive skin tests to one or more pollens, especially to giant or short ragweed, the chief causes of hay fever in this region. As a rule the dyspnea in this group occurred about one week after the hay fever symptoms began and some of the cases were acutely ill at this time.

The other 54 positive cases of bronchial asthma gave 126 positive skin tests to different substances. There were 64 positive to animal derivatives, 23 to food substances, 23 to house dust, and 16 to miscellaneous substances. From this number it is at once apparent that most cases are sensitive to more than one substance and this fact emphasizes the necessity of complete testing of patients. It is not advisable to quit trying when one positive is found.

Of the animal materials goose, duck and chicken feathers comprise 25 of the positives; cat hair 8; horse dander 7; cattle hair 5; pigeon feathers and squirrel fur 4 each; canary feathers 3; 2 each of dog hair, camel hair, and rabbit hair; one each of mouse hair and parrot feathers.

The food substances were scattered and not nearly so important, but did include 3 cases each of egg and wheat which are frequent causes of bronchial asthma. The other 17 food positives were divided among the vegetables, chiefly, and were apparently of little importance as causative factors.

The miscellaneous group had 16 positives, chief of which was orris root, the basis of face and talcum powders—there were 7 positives to this. Py-

rethrum, the main ingredient of insect powders, was second with 4; the other 5 consisted of 1 positive for each of silk, tobacco, kapok (silk floss) henna and face cream.

There were 23 positive tests for house dust. Dust was collected from several houses and extracted according to the Coca method and injected intracutaneously, using a control of the extracting fluids. Dust is obviously a mixture and as obviously must vary more or less in different homes. Up to the present time we have not had facilities for collecting and extracting dust from each patient's home. This is the ideal we have in mind and will carry out as soon as we have sufficient assistance. We approached this work about a year ago in a very skeptical frame of mind even though some excellent results had been reported from the Cornell clinic. We have had some encouraging results, however, and the work is still going on.

The treatment carried on in the clinic is both symptomatic and specific. The former consists of adrenalin and ephedrin for attacks of asthma; cough mixtures, potassium iodide, calcium lactate, thyroid, etc. The specific treatment aims at elimination of the offending substance, where possible, and desensitization where necessary. Pillows are banished in the feather cases; animals in those affected by them; eggs and wheat are withdrawn from the diet where indicated; face powder removed in those cases sensitive to orris root. We have used ephedrin in about 75 cases to date and can say we have had some fairly good results and some not so good. With better grade ephedrin now available we hope for better success.

Desensitization has been attempted, where advisable, by increasing hypodermic injections of the offending substances—beginning with 0.1 c.c., usually, of 1:10,000 or 1:100,000 dilution and working up to 1:500 or in pollens, to 1:100 dilution. Altogether about 20 to 30 injections or more have been given in each case. Dust injections have been given beginning with 0.05 c.c. and increasing the same amount each time till 1 c.c. dosage has been reached; then we repeat this dose once or twice weekly.

In certain cases, especially in those who gave no positive skin tests, other measures have recently been tried, including vaccine therapy, mercury quartz vapor lamp and x-ray treatments and intravenous injections of sodium iodide and calcium chloride. The work along these lines is too new for definite reports but we feel strongly that autogenous vaccine and quartz lamp treatments offer considerable promise. We hope to report on these aspects at some future time.

The hay fever cases have been given both preseasonal and coseasonal injections of the offending pollens and we have had good results in both groups. We prefer to give treatment before the time of pollenation but in those patients who report during the season we have been agreeably surprised at some excellent results from a few injections.

The results of treatment in our asthma and hay fever cases have been as follows:

BRONCHIAL ASTHMA	121 CASES
Good results	12
Improved	26
Not improved	7
Not returned or incomplete	76

Of the patients who showed positive skin tests and who have more or less completed treatment 35 out of 38 showed at least some improvement. Of these 10 were rendered practically free from asthma.

Three of seven asthma patients who were thoroughly tested and found negative were somewhat improved by symptomatic treatment; four cases still have attacks.

HAY FEVER	47 CASES
Good results	14
Improved	11
Not improved	1
Treatment incomplete	21

Thus we find 25 of 26 completed cases more or less improved by preseasonal or coseasonal pollen injections, we especially noted that those cases with combined asthma and hay fever were most benefited by this treatment and practically every one was rendered free from asthma.

ALLERGIC RHINITIS

This condition is characterized by more or less sneezing and rhinitis occurring all year round. Pollen tests are usually negative here while tests for orris root, feathers or wheat flour are frequently positive. Removal of the cause and desensitization usually give excellent results. We had only four cases of this affection of whom three were sensitive to orris root, and one to wheat. There is no doubt that a large percentage of persons, especially women, who have frequent attacks of rhinitis belong to this sensitive group; and, likewise, if physicians who treat these cases would have them skin-tested many more would be unearthed, their offending substance or substances removed, and the patients benefited.

There were five cases of urticaria and angioneurotic edema. Skin tests were negative in one and tests were incomplete or not done in three. One splendid result occurred lately; a woman strongly positive to silk. She has improved remarkably on withdrawal of all silk garments.

Of 189 patients 38 were definitely nonallergic and in most of these skin tests were not carried out. In the few tested no positives were found. Of these 38, 13 were diagnosed cardiorenal cases and gave the the usual history of dyspnea on exertion beginning late in life and associated with abnormal heart or kidney findings. There were six cases of tertiary syphilis, possibly syphilis of the lung; these were most interesting cases and some had severe asthma closely simulating bronchial asthma. Specific luetic treatment was given these patients with some very excellent results.

Three cases were diagnosed pulmonary tuberculosis. This is a small number when we realize that a large percentage of all asthma cases are wrongly diagnosed as tuberculous and many of our cases have been in sanatoriums. From our experience we would suggest that a patient having attacks of cough, wheezing, and dyspnea who has asthmatic type of râles only, and who has had repeated negative sputums, is probably not tuberculous and should be tested for bronchial asthma.

One disagreeable fact stands out in this brief review and that is the large number of cases who have not returned for further testing. Some came only once, others only a few times. This feature is characteristic of all dispensary work and exists to a lesser extent in private practice as well. Patients wander around from clinic to clinic as they often do from one physician to another. We have wasted a good deal of time and strength caring for these cases with no apparent good either to them or to us.

In an effort to lessen this evil we now hand each new case a copy of the following *Instructions to Patients Suffering with Asthma.* "Asthma is a chronic ailment and one which causes a good deal of suffering. We know that among the chief causes of asthma are hair and dander from animals, foods, pollens from weeds, bacteria and dust.

"A great deal of time and patience is required to discover the cause in any one particular case and then there follows a long course of treatment which depends on the cause in each case. All this takes time but in order to get good results in this long drawn out sickness *we must have your help.* You must be patient and come regularly when told to do so.

"If you do not intend to go through with the tests and treatment we carry out here, we prefer that you do not begin at all as we do not want to waste your time or ours. The results here have been excellent in most cases; if you cooperate and follow instructions you also have a good chance to obtain relief."

We hope the above pamphlet will help our attendance.

In conclusion I want to thank Drs. S. M. Feinberg and S. J. Taub for their invaluable services both in the clinic and in preparing these statistics. We trust that at some future time we may again have the opportunity to come before you with some newer and more important discoveries.

THE RÔLE OF THE STRUCTURAL FEATURES OF POLLEN GRAINS IN IDENTIFYING THE MOST IMPORTANT HAY FEVER PLANTS OF CALIFORNIA*

By George Piness, M.D., and H. E. McMinn, A.B., A.M., Los Angeles

INTRODUCTION

ATTEMPTS at identifying wind-blown pollens have been made by various workers in the field of allergy. The pollen is secured by exposing microscopic slides covered with a thin layer of glycerin, corn oil, or cottonseed oil. Most of these attempts have been very limited on account of the almost total absence of structural keys for the identification of the pollens found upon the slides.

During the past three years we have made studies of about 350 species of wind-blown pollen plants of California. The pollens from about 180 of these species have been included in the treatment of allergic patients in our laboratories. The structural features of these pollens have been carefully studied, and a key has been prepared which will enable us to determine, as far as possible, the species of plants whose pollens might be found in the atmosphere throughout the state of California.

METHODS

The pollens were examined fresh from the flowers, several days after falling, and after being treated with ether. These three pollen conditions were designated as fresh, dry and ether-dry respectively. Observations were made with the aid of the 4 mm. and oil immersion objectives upon the three pollen conditions, mounted dry, in water and in balsam. Dry and ether-dry pollens when mounted dry were similar in all visible characteristics with the exception of color, whereas the fresh pollen mounted dry varied much in shape and in other visible characteristics, this being due perhaps to the amount of desiccation occurring before and during shedding. Water and balsam mounts caused most dry and ether-dry pollen to become spherical, exceptions being noticed in a few species with oval, elliptical and pyradimal pollen grains. These simply swelled slightly, retaining their characteristic shape when dry.

Water mounts proved the most valuable in studying the germinal pores and certain features of the exine, while dry mounts were used for the study of size, shape and furrows caused by desiccation. We have considered the dry condition the natural condition of pollen for our studies because the pollen, when wind-blown, soon becomes desiccated and shrunken. This is in agreement with the studies of Pope.[4]

Photomicrographs were made of all pollens and these aided materially in supplmenting the microscopic observations.

*Read before the American Association for the Study of Allergy, Washington, D. C., May 17, 1927.

RESULTS

Although most of our results are embodied in the key which follows, it seems important to call attention to a few outstanding observations and conclusions. The grass family, Gramineae, contains more possible hay fever species than any other plant family. Over thirty genera, including about seventy species, of grass pollens were studied. Dry mounts of dry pollen revealed that all species of grasses contained many pollen grains resembling in shape and appearance grains of half-ripe field corn, i.e., pyramidal with shrunken cavities on their surfaces. This character, while not uniformly present in all pollen grains, serves as one of the best aids in identifying grass pollens. Without a single exception all the species showed a single germinal pore and the presence of abundant starch. These characteristics showed up particularly well when mounted in a weak solution of iodine in aqueous potassium iodide.

The mean average length of the dry grains was 37.5 microns, the range extending from 18 microns in Sporobolus airoides to 58 microns in Secale cereale. A variation of 7 to 10 microns was found in the various samples of a given species. Size alone proved of very little aid in identifying pollens.

In the sunflower family, Compositae, two distinct types of pollen grains were found, a spherical or oval form with definite spicules and an elliptical form with furrows. The latter form was characteristic of all species of the genus Artemisia, the former of all the genera of the tribe Ambrosiaceae. In both forms the surface of the pollen grains appeared slightly granular or roughened as in an orange peeling. Water mounts of all species of Artemisia were spherical in general outline yet distinctly three-lobed, the lobes representing the exine surfaces between the longitudinal furrows.

The number and size of the spicules were found to be quite variable among all the species of the tribe Ambrosiaceae. Species of some genera, however, resembled each other so closely in spicule characters that it was impossible to distinguish the species in a mixed mount. This was found to be the case also among the genera of Ambrosiaceae. Since in many localities of California the ragweeds (ambrosias), franserias and cockleburs shed their pollen concurrently, it would be highly doubtful whether one could rely upon specific or even generic identification of the spiculated pollen grains found upon exposed plates. It would be fairly safe to state, however, that all wind-blown pollens with spicules belonged to the Ambrosiaceae, as no other strictly wind-blown pollens possess this characteristic. All the varieties of baccharis, cosmos, coreopsis, chrysanthemum, gaillardia and helianthus have spicules, but these genera of Compositae, being primarily insect-pollinated, can scarcely be expected to appear upon a pollen plate.

The third largest family considered was the goosefoot or chenopod (Chenopodiaceae) family. All the species possessed spherical pollen grains. The exine showed distinct round concavities, giving the pollen grains the appearance of "round mesh" golf balls. These concavities or depressions varied in size and number among the different genera and among the species of a given genus. Since a given sample of pollen from a single species of a chenopod showed considerable variation in number and size of these concavities, it was

TABLE I

SUMMARY OF POLLENS STUDIED

FAMILY	NUMBER OF GENERA	NUMBER OF SPECIES	SHAPE WHEN DRY	EXTERNAL MARKINGS AND OTHER FEATURES. OBSERVED DRY AND MOIST. SHAPE WHEN MOIST.
Aceraceae †Maple	1	2	Elliptical, with furrows.	Smooth. Spherical, somewhat 3-lobed.
Amaranthaceae †Amaranth	1	4	Spherical, sometimes irregular.	With regularly arranged concavities, like round-mesh golf balls. Slightly granular. Spherical.
Betulaceae †Birch	3	4	Polyhedric	Pores at the thickened corners. Irregularly spherical. 3 to 5 germinal pores.
Chenopodiaceae †Chenopod	7	19	Spherical	With concavities or pores, like round-mesh golf balls. Granular or smooth. Starch present. Spherical.
Compositae *Sunflower	11	26	Artemisia — Elliptical with furrows. Other Genera—Oval or spherical.	Artemisia—Smooth or very granular. Spherical, 3-lobed. Other Genera—Spiculate. Spherical or oval.
Cruciferae *Mustard	1	2	Elliptical, with furrows.	Granules forming regular reticulations. Oval.
Cyperaceae †Sedge	2	2	Irregularly spherical, oval, pyramidal. Shrunken surfaces.	Carex—Smooth, oval. Scirpus—Smooth, pyramidal.
Euphorbiaceae *Spurge	1	1	Irregularly oval or spherical. Shrunken surfaces.	Smooth and spherical.
Fagaceae †Beech or Oak	3	8	Elliptical, with furrows.	Smooth or slightly granular. Spherical or broadly elliptical. 3 germinal pores.
Garryaceae †Silk-tassel	1	2	Irregularly spherical.	Granular or reticulated. Spherical. 3 germinal pores.
Gramineae †Grass	33	68	Irregularly oval, spherical, pyramidal. "Grain corn-like" with shrunken surfaces.	Smooth. One germinal pore. Starch present. Spherical or broadly elliptical or pyramidal.
Juglandaceae †Walnut	1	3	Irregularly spherical.	10 to 14 larges pores. Scalloped around edge. Spherical.
Leguminoseae *Pea	1	8	Spherical to oval.	With concentric polygons over surface. Spherical.
Moraceae *Mulberry	2	2	Irregularly oval to elliptical with shrunken surfaces.	Humulus—Smooth, with 3 pores. Spherical. Morus—Smooth, with a pore at each pole. Spherical.
Myricaceae †Sweet-gale	1	1	Polyhedric. Shrunken surfaces.	Smooth. 3 germinal pores. Spherical—somewhat 3-lobed.
Myrtaceae *Myrtle or Eucalyptus	1	2	Equilaterally triangular with retusely-truncated corners.	Similar to dry, but swollen.

*Insect and wind pollinated.
†Wind pollinated.

TABLE I—CONTINUED

SUMMARY OF POLLENS STUDIED

FAMILY	NUMBER OF GENERA	NUMBER OF SPECIES	SHAPE WHEN DRY	EXTERNAL MARKINGS AND OTHER FEATURES. OBSERVED DRY AND MOIST. SHAPE WHEN MOIST.
Oleaceae †Olive	1	1	Broadly elliptical.	Very granular or reticulated. Spherical.
Palmaceae †Palm	1	2	Elliptical with 1 furrow and acute ends.	Smooth. Irregularly spherical.
Papaveraceae *Poppy	1	1	Spherical.	Smooth. Spherical. Orange color. With 6 narrow furrows.
Pinaceae †Pine	1	2	Spherical, with wings.	Smooth. Shape same as when dry.
Plantaginaceae †Plantain	1	3	Irregularly spherical, with shrunken surfaces.	Smooth. With 10 to 14 germinal pores. Starch present. Spherical.
Platanaceae †Plane Tree	1	2	Truncated elliptical.	Finely granular like an orange peeling. Spherical.
Polygonaceae †Buckwheat	2	6	Irregularly oval to elliptical — variable, with irregular folds or furrows.	Smooth. Large, abundant starch granules. Spherical.
Rosaceae *Rose	1	1	Irregularly spherical to elliptical.	Smooth. Spherical. 3 germinal pores.
Salicaceae *Willow	2	5	Salix—Broadly elliptical, with 3 furrows.	Salix—Reticulated, except in furrows. Spherical.
			Populus — Irregularly spherical.	Populus—Smooth. Spherical.
Sparganiaceae †Bur-reed	1	1	Irregularly spherical to elliptical with folds or creases.	Granular all over surface. Little starch. Spherical.
Typhaceae †Cat-tail	1	2	Typha Angustifolia—Irregularly spherical or oval.	T. Angustifolia—Granular all over like an orange peeling. Spherical.
			Typha Latifolia—In tetrads (groups of four).	T. Latifolia — Granular. In tetrads.
Umbelliferae *Parsnip	1	1	Peanut-shaped	Smooth. Elliptical with 4 pores at middle, often protruding.
Urticaceae †Nettle	1	1	Irregularly oval or pyramidal, with shrunken surfaces.	Smooth. With 3 germinal pores. Spherical.

concluded that these characteristics were not suitable criteria for distinguishing the different genera and species of the Chenopodiaceae. The entire surface was either smooth or slightly roughened as in an orange peeling.

Very closely related, taxonomically, to the chenopods are the Amaranths (Amaranthaceae). Their pollens were similar to those of the chenopods in all observed morphologic features. Since several species of the Chenopodiaceae and Amaranthaceae shed their pollen during the same season and since they are quite likely to be growing in the same vicinity, we might, therefore, ex-

pect to find these pollens mixed on the same pollen plate. But with our present knowledge of pollen morphology it seems quite impossible to identify these pollens from a given mixture of species. In the case of these two plant families the cleavage line of pollen differentiation is broader than a single family, while in the Compositae the cleavage line was within the family and in the Gramineae it was coextensive with the family.

The mean average diameter of the pollen from the species of Chenopodiaceae was 23 microns and for those of Amaranthaceae 24 microns. The range of variation was from 17.87 microns to 30 microns. But since single pollen grains of a given species vary as much as 10 microns in size, it would be presumptuous to say that one could separate the species of these two families by the size of their pollen grains.

All the other pollens studied grouped themselves into 29 families including 33 genera and 59 species, but no single family included a sufficient

Explanation of Figures

Figs. 1 to 18 inclusive are photomicrographs of dry pollen grains X 720, showing all the different shapes and gross features found in our studies.

Figs. 19 to 34 inclusive are drawings of dry and moist pollen grains showing shapes and more minute features.

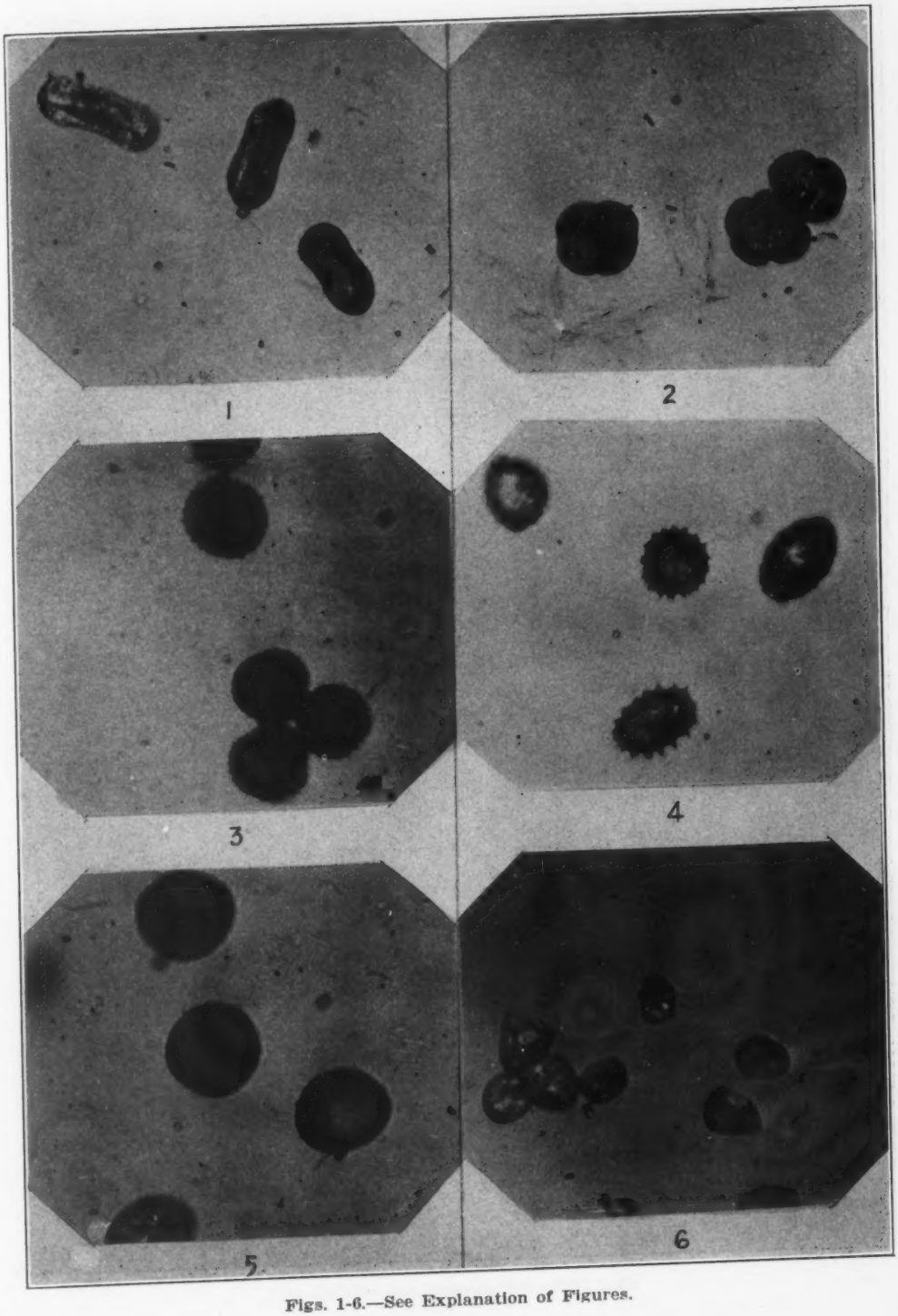
Fig. 1.—*Foeniculum vulgare gaertn.*, showing peanut-shaped grain. Fig. 2.—*Typha latifolia L.*, pollen grains in tetrads. Fig. 3.—*Franseria acanthicarpa Hook*, spherical with spicules. Fig. 4.—*Baccharis pilularis D C.*, oval with coarse spicules, almost spinose. Fig. 5.—*Xanthium canadense Mill.*, spherical with very fine spicules almost only coarsely granular. Fig. 6.—*Urtica gracilis var. holosericea Jepson*, showing irregularly oval, spherical and pyramidal shapes with shrunken surfaces.

Fig. 7.—*Alnus rhombifolia Nutt.*, polyhedric. Fig. 8.—*Scirpus acutus Muhl.*, elongated pyramidal with acute apex. Fig. 9.—*Phleum pratense L.*, with shape of grain of corn with shrunken surfaces and obtuse or rounded corners. Fig. 10.—*Phalaris canariensis L.*, showing single germinal pore. Fig. 11.—*Phoenix canariensis Hort.*, elliptical with a single furrow and acute ends. Fig. 12.—*Artemisia campestris pycnocephala Hall*, elliptical with two furrows (one visible) and rounded ends.

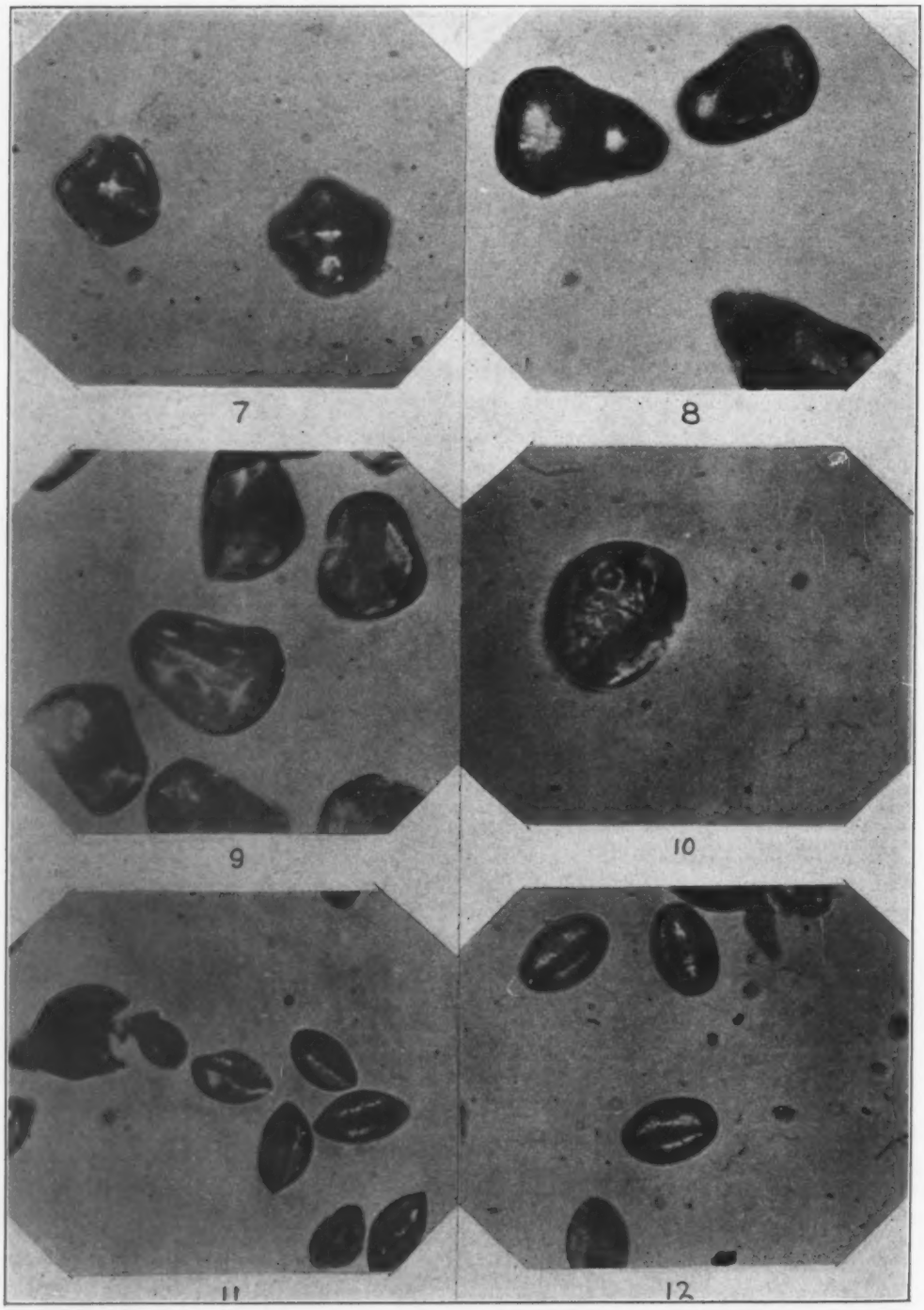
Fig. 13.—*Platanus occidentalis L.*, elliptical with truncate ends, slightly granular. Fig. 14.—*Olea europea L.*, broadly elliptical with granular or reticulate surface. Fig. 15.—*Atriplex rosea L.*, like round mesh golf balls, characteristic of all Chenopodiaceae. Fig. 16.—*Amaranthus retroflexus L.*, showing similarity to Chenopodiaceae. Fig. 17.—*Juglans californica Wats.*, spherical with scalloped edge in median optical view and numerous pores in surface view. Surface view of pollen grain (upper left hand corner) showing depressions. Fig. 18.—*Sparganium eurycarpum var. greenei Graebner*, spherical (moist) with very granular surface.

Fig. 19.—*Eschscholtzia californica Cham.* X 750, moist mounts. *a*, Median optical polar view showing thin perine and six narrow, expanded furrow bands. *b*, Polar surface view showing six narrow furrow bands not reaching the pole. Fig. 20.—*Salix lasiolepis Benth.* X 1400. Dry mount showing elliptical pollen grain with rounded ends, two longitudinal folds, and reticulated surface. Fig. 21.—*Morus alba L.* X 1400. Moist mount, median optical view showing thin perine and two polar germinal pores. Fig. 22.—*Quercus agrifolia Nee.* X 1200. Moist mounts. *a*, Median optical polar view showing intine protruding through pores in exine. *b*, Polar surface view showing fine granules and three protruding portions of intine. Fig. 23.—*Plantago lanceolata L.* X 1000. Moist mount showing distantly placed germinal pores (10 to 14 to each grain). Fig. 24.—*Urtica gracilis var. holosericia Jepson.* X 1000. Dry mount showing irregular shapes and shrunken surfaces and furrows. Fig. 25.—*Artemisia vulgaris heterophylla Hall.* X 1400. *a*, Dry mount surface view showing elliptical shape with furrow and smooth surface. *b*, Dry mount polar surface view showing three narrow, longitudinal furrows not reaching the pole. *c*, Moist mount, polar median optical view, 3-lobed, showing 3 crescent-shaped sections of perine united end to end, and the intine protruding through the 3 pores found in thin places between two adjacent perine sections.

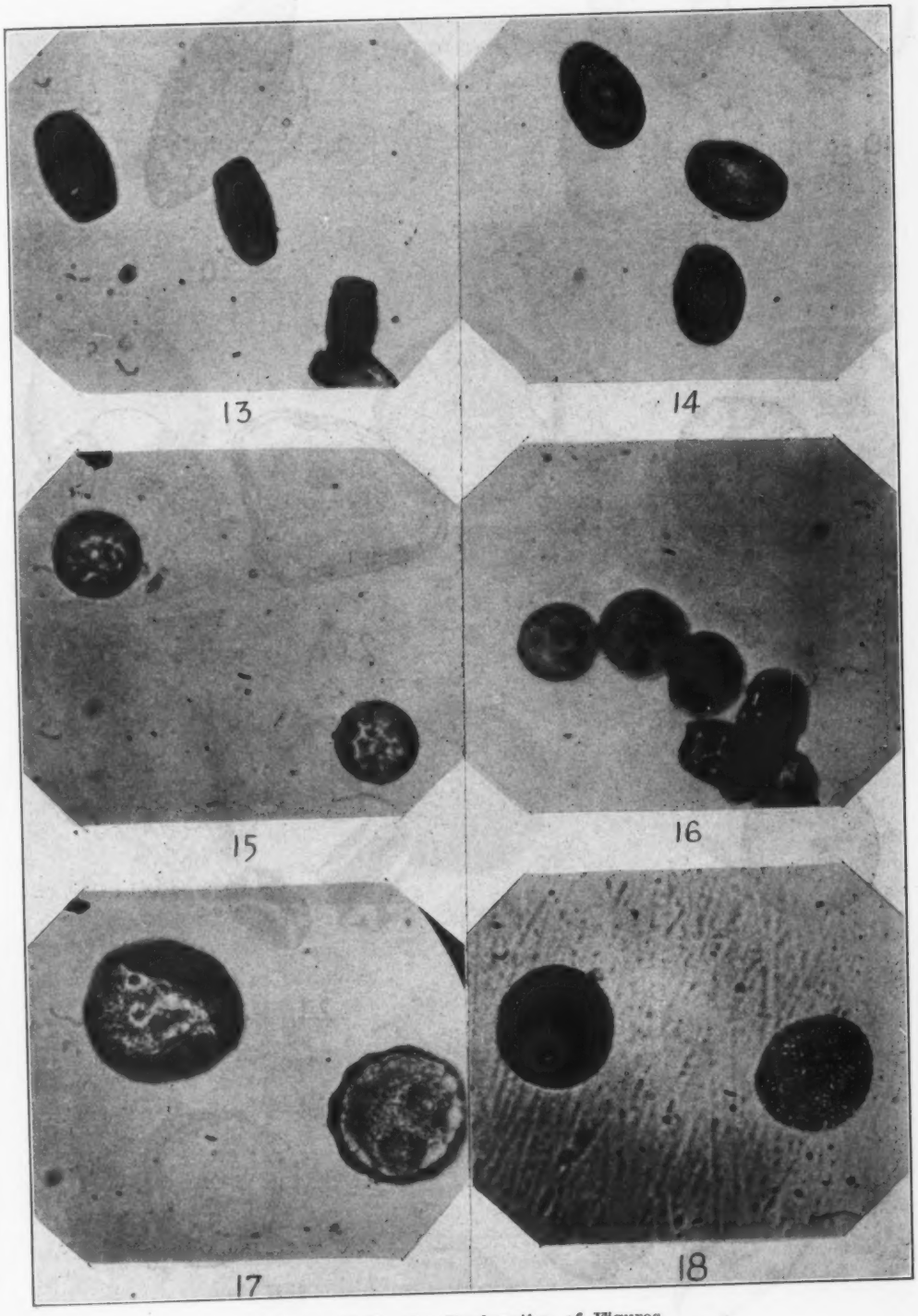
Fig. 26.—*Rumex acetosella L.* X 1000. Moist mount showing spherical shape, thin perine, and abundant large starch grains. Fig. 27.—*Corylus rostrata var. californica A. DC.* X 1000. Moist mount polar median optical view showing three germinal pores through the thickened corners and vacuoles beneath the pores. Fig. 28.—*Humulus lupulus L.* X 1200. Moist mount, surface view showing 3 germinal pores resembling bordered pits of the tracheids of pine. Fig. 29.—*Alnus rubra Bong.* X 1000. Moist mount, polar median optical view showing 5 germinal pores and vacuoles beneath the pores. Fig. 30.—*Festuca californica Vasey*, X 1000. Moist mount showing spherical shape and the single germinal pore. Fig. 31.—*Pinus radiata Don.* X 800. Moist mount showing lateral wings. Fig. 32.—*Garrya elliptica Dougl.* X 1120. Moist mounts. *a*, Surface view showing reticulations. *b*, Polar median optical view showing 3 germinal pores and perine sections of approximately equal thickness. Fig. 33.—*Acacia melanoxylon R. Br.* X 600. Dry mount showing concentric polygons over surface. Fig. 34.—*Eucalyptus globulus Labill.* X 1200. Equilaternally triangular with retusely truncated corner.



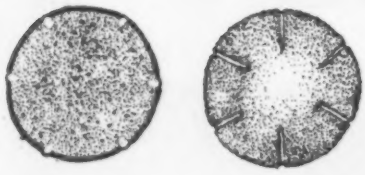
Figs. 1-6.—See Explanation of Figures.



Figs. 7-12.—See Explanation of Figures.

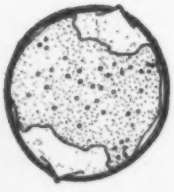


Figs. 13-18.—See Explanation of Figures.

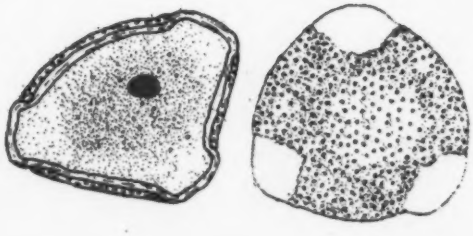


19 a b

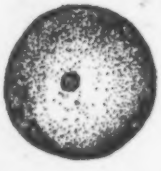
20



21



22 a b



23

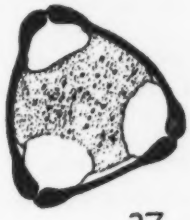
24

25 a b

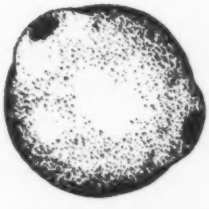
c

Figs. 19-25.—See Explanation of Figures.

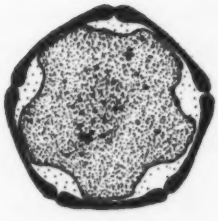
26



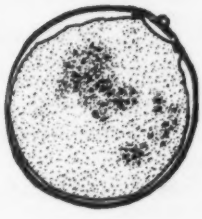
27



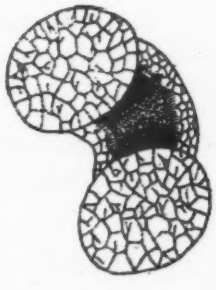
28



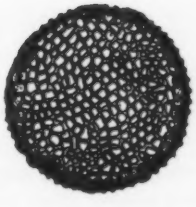
29



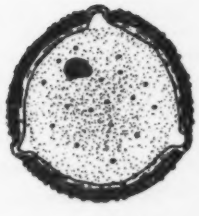
30



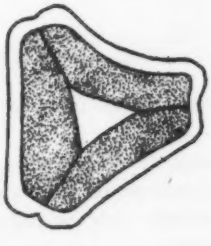
31



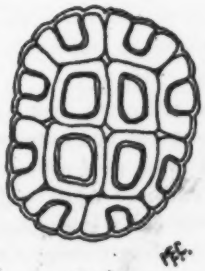
32 a



32 b



33



34

Figs. 26-34.—See Explanation of Figures.

number of genera or species to warrant more than the specific conclusions given in the summary of families in Table I.

KEY TO POLLENS

Shapes and other characteristics refer to dry pollen grains unless stated otherwise.

The mean average size of the pollen grains have been obtained from 10 to 100 counts of dry pollen. A variation from 5 to 10 microns may be expected among the grains of the same species.

A careful study of the figures and photomicrographs will aid in understanding the terminology used.

A knowledge of the plants in the district from which the pollens are secured will aid in verifying the identification made by use of the key.

I. Peanut-shaped (Fig. 1); mean average length 28 microns; summer and autumn. *Foeniculum**

II. In tetrads (Fig. 2) (groups of 4); mean average diameter for the tetrads 37 microns. *Typha latifolia*

III. With 2 lateral wings (Fig. 31). *Pinus*

IV. With concentric polygons (Fig. 34) all over the surface; spherical to oval; mean average length 40 microns; spring. *Acacia*

V. Equilaterally triangular with retusely-truncated corners (Fig. 33); not spherical when moist. *Eucalyptus*

VI. With distinct spicules (Fig. 3) or spines, or rarely apparently only coarsely granular (Fig. 18).

A. Oval (Fig. 4) or broadly elliptical (Fig. 14).

1. Coarsely spinose; mean average length 35 microns. *Helianthus**

2. Coarsely spinose; mean average length 49 microns. *Gaillardia**

3. Distinctly spiculate (Fig. 3) but not spinose; oval.

a. Mean average length 30 microns; from cultivated flowers. *Cosmos**, *Chrysanthemum**

b. Mean average length 25 microns; from wild shrubs of coast ranges, Oregon southern California; autumn *Baccharis pilularis**

4. Coarsely granular (Fig. 14) or reticulate.

a. Broadly elliptical (Fig. 14) or oval; mean average length 27 microns; end view 3-lobed; spring. *Olea*

b. Irregularly spherical or oval; end view not 3-lobed. *Sparganium*

B. Spherical (Fig. 5).

1. From cultivated, insect-pollinated flowers; mean average diameter 21 microns; summer and autumn. *Coreopsis**

2. From wild wind-pollinated plants; range in mean average diameter 17 to 29 microns; April to November (Ambrosieae tribe of the family Compositae).

a. Very finely spiculate (Fig. 5), apparently only coarsely granular.

(1). Mean average diameter 29 microns. *Xanthium canadense*

(2). Mean average diameter 24 microns. *Franseria bipinnatifida*

b. Distinctly spiculate (Fig. 4).

(1). Mean average diameter 17 to 25 microns. *Ambrosia, Franseria, Iva and Xanthium spinosum*

VII. Without spicules or spines.

A. Elliptical or oval; with regular longitudinal folds (Fig. 25) or furrows.

1. With one longitudinal furrow (Fig. 11) extending from pole to pole; ends acute; smooth when moist.

a. When moist, three germinal pores evident, resembling bordered pits (Fig. 28) in tracheids of pine; mean average diameter 24 microns.

Humulus lupulus

b. When moist, germinal pores not evident; mean average diameter 17 microns.

Phoenix

2. With 3 longitudinal furrows (Fig. 20) between the poles, only 1 or 2 visible at a given focus.

a. Surface distinctly reticulated (Fig. 20); ends rounded (Fig. 12).

(1). Becoming spherical when moist; mean average length 27 microns.

(a) When moist, reticulated (Fig. 14) all over the surface, longitudinal furrow-bands not evident. *Olea*

(b) When moist, not reticulated on furrow-bands, these very evident. *Salix*

(2). Becoming oval when moist; mean average length 42 microns. *Brassica**

b. Surface not reticulated; apparently somewhat granular.

(1). With truncate ends (Fig. 13).

(a). When moist, with large abundant starch grains (Fig. 26) evident, germinal pores not evident. *Rumex*

(b). When moist, without large abundant starch grains, furrows and pores evident.

(aa). Mean average length less than 30 microns, typically 23 microns; perine, when moist, apparently of same thickness (Fig. 32-b) all around, granular on furrow bands as well as over surface. *Platanus*

(bb). Mean average length typically 35 to 40 microns; perine, when moist, thinner in the 3 furrow bands, these expanded, smooth, not reaching the poles; when moist 3 protruding germinal pores (Fig. 22-a) on bands, mid-polar. *Quercus*

(2). With rounded ends (Fig. 12).

(a). Mean average length 20 microns; becoming broadly elliptical when moist, with 3 germinal pores mid-polar. *Castanopsis*

(b). Mean average length 24 to 55 microns; becoming spherical when moist, often with three prominent lobes.

(aa). When moist, with large abundant starch grains evident; furrows and pores not evident. *Rumex*

(bb). When moist, large abundant starch grains not evident; furrows evident as bands on perine, not reaching the poles (Fig. 25-b).

(aaa). Perine, when moist, in median optical view of unequal thickness, appearing as 3 crescents (Fig. 25-c) united end to end forming a circle, with a pore at the thin place between 2 adjacent crescent-shaped portions of perine. *Artemisia*

(bbb). Perine, when moist, in median optical (Fig. 32-b) view of nearly equal thickness all around.

(1,1). Pores evident in moist mounts. *Ricinus*

(2,2). Pores not evident in moist or dry mounts.

Mean average length 55 microns.

Acer macrophyllum

Mean average length 35 microns.

Acer negundo var. californicum

B. Irregularly spherical (Fig. 6), oval (Fig. 6), pyramidal (Fig. 6) or polyhedric (Figs. 6, 7); with shrunken depressions (Figs. 6, 7) on surface or with irregular folds due to irregular collapsing of the walls during dessication as in a dried prune.

1. Many grains typically with shape of grain of corn (Fig. 9) with obtuse corners, i.e. broadly pyramidal (Fig. 9); surface with shrunken depressions; *all grains with an evident germinal pore when moist* (Fig. 10, 30).

All species of grass, *Gramineae;*
Without evident germinal port when moist,
Carex and *Scirpus* in *Cyperaceae*
Scirpus (Fig. 8) pollent grains are not spherical when moist.

a. Mean average length 17 to 20 microns. *Sporobolus airoides* 18.5

b. Mean average length 21 to 30 microns.

Agrostis diegoensis,	30 microns	Melica torreyanna,	30 microns
A. palustris,	27 "	Phalaris lemmoni,	28 "
A. verticillata,	30 "	Poa annua,	24 "
Capriola dactylon,	29 "	P. pratensis,	30 "
Festuca rubra,	30 "	Puccinellia nuttalliana,	26 "
Melica bulbosa,	27 "	Syntherisma sanguinalis,	28 "

c. Mean average length 31 to 40 microns.

Ammophila arenaria,	37 microns	Lolium temulentum,	36 microns
Arrhenatherum elatius,	39 "	Melica imperfecta,	33 "
Bromus hordeaceus,	40 "	Notholcus lanatus,	32 "
B. laevipes,	31 "	Oryzopsis miliacea,	31 "
Dactylis glomerata,	36 "	Paspalum distichum	38 "
Distichlis spicata,	36 "	Phalaris canariensis,	36 "
Danthonia californica,	34 "	P. paradoxa,	38 "
Echinochloa crus-galli,	38 "	Phleum pratense,	33 "
Festuca elatior,	33 "	Poa scabrella	32 "
F. megalura,	34 "	Poa unilateralis,	36 "
F. myuros,	32 "	Polypogon lutosus	35 "
Koeleria cristata,	36 "	P. monspeliensis,	37 "
Lolium multiflorum,	36 "	Stipa lepida,	34 "
L. perenne,	39 "	Sitanion anomalum	38 "

d. Mean average length 41 to 58 microns.

Avena barbata,	45 microns	Bromus rigidus,	49 microns
A. fatua,	56 "	B. rubens,	41 "
A. sativa,	56 "	Elymus condensatus,	47 "
Bromus carinatus,	41 "	E. glaucus,	45 "
B. marginatus,	44 "	E. triticoides,	51 "
Festuca californica	43 to 53 microns.	Phalaris minor,	43 "
Holcus sorghum,	42 "	P. stenoptera,	47 "
H. halepensis,	45 "	Secale cereale,	58 "
H. halepensis var. sudanensis,	43 "	(becoming oval when moist)	
Hordeum murinum,	48 "	Setaria glauca,	46 "
H. nodosum,	45 "	Sitanion jubatum,	42 "
H. vulgare,	47 "	Stipa pulchra,	42 "

2. With irregular folds; *when moist, one germinal pore* (Fig. 21) *visible at either pole;* mean average diameter 17 microns. *Morus*

3. *When moist,* 3 *germinal pores* (Fig. 32-b) visible, equidistantly placed.

a. Mean average diameter 14 microns. *Adenostoma**

b. Mean average diameter, or length, 18 microns; with shrunken (Fig. 6) surface. *Urtica*

c. Mean average diameter, or length, 24 microns or more; surface shrunken as in a dried prune.

(1). When moist, the intine protruding through the 3 germinal pores of the very thin exine, appearing as bordered pits (Fig. 28) in tracheids of pine, mean average diameter 24 microns; dry, length 28 microns. *Humulus lupulus*

(2). When moist, intine not protruding through the 3 germinal pores, nor appearing as bordered pits in tracheids of pine.

(a). 3 furrows expanded when moist, appearing as narrow, longitudinal bands not reaching the poles; dry, mean average length 35 microns. *Ricinus*

(b). Furrows not visible; when moist, the 3 pores, if visible, in thickened corners (Fig. 27).

(aa). Mean average diameter 28 microns; February-March. *Corylus*

(bb). Mean average diameter 25 microns; March-April. *Myrica*

4. With 4 or 5 germinal pores (Fig. 29) at the thickened corners of the perine.

a. Mean average diameter 24 microns. *Alnus rhombifolia*

b. Mean average diameter 28 microns. *Alnus rubra, Betula.*

5. When moist or dry, with 10 to 14 evident germinal pores (Fig. 23) equidistantly placed over surface (4 to 6 in a single focus view); apparently granular when dry, smooth when moist; mean average diameter when moist 25 microns. *Plantago*

6. When moist or dry, without evident germinal pores.

a. Typically dessicated spheres with irregular folds, or broadly elliptic with regular furrows.

(1). When moist, with large abundant starch grains (Fig. 26) and 3 furrows appearing as narrow, longitudinal bands not reaching the poles. *Rumex*

(2). When moist, without large abundant starch grains and furrows appearing as longitudinal bands.

(a). Granular (Fig. 18) or reticulated. *Sparganium*

(b). Not granular or reticulated. *Populus*

b. Typically polyhedric (Fig. 7), 3-4-, or 5-angled in median optical polar view, showing as many lobes when moist or almost spherical, with thickened perins at corners; *when moist, without evident large abundant starch grains.*

(1). With 3 or 4 corners; when moist, in median optical (Fig. 29) polar view, with 3 blunt corners, *vacuolate* (Fig. 27) *beneath the corners;* mean average diameter 28 microns.

(a). Mean average diameter 24 microns. *Alnus rhombifolia*

(b). Mean average diameter 28 microns. *Alnus rubra, Betula*

C. Spherical.

1. With regular concavities (Fig. 15) or large pores, like round-mesh golf balls; granular. *Baccharis pilularis*[5]

a. Mean average diameter less than 20 microns.

Allenrolfea occidentalis, Amaranthus graecizans, and Beta vulgaris

b. Mean average diameter 20 to 25 microns.

Amaranthus, Atriplex, Chenopodium Sasola and *Suaeda*

c. Mean average diameter 27 to 30 microns.

Chenopodium californicum, Suaeda californica, Suaeda moquini, and *Amaranthus palmeri* in the Imperial Valley.

d. Mean average diameter 36 to 44 microns; pores distantly (Fig. 17) placed, not distinctly golf-ball-like as in Chenopodiaceae and Amaranthaceae, but may be confused with that family except for size. *Juglans*

2. Without appearance of round-mesh golf balls.
   a. Mean average diameter 14 microns. *Adenostoma**
   b. Mean average diameter over 20 microns.
      (1). Distinctly granular or reticulated (Fig. 32-a) all over the surface like an orange; not scalloped around the the edge.
         (a). 3 germinal pores evident when moist.
            (aa). With irregular folds or creases when dry; mean average diameter 35 microns. *Ricinus*
            (bb). Without evident folds or creases when dry.
               (aaa). Mean average diameter 29 microns. *Garrya elliptica*
               (bbb). Mean average diameter 35 microns. *Garrya fremontiti*
         (b). Germinal pores not evident when moist or dry.
            (aa). With evident irregular folds or creases; mean average diameter 25 microns. *Sparganium*
            (bb). Without evident irregular folds or creases; mean average diameter 28 microns. *Typha angustifolia*
      (2). Not granular like an orange, but with 10 to 14 large depressions with a pore in each; scalloped (Fig. 17) around the edge in median optical view; mean average diameter 36 to 44 microns. *Juglans regia*, 36 microns
      Juglans californica, 44 microns
      (3). Smooth rarely apparently granular; without scalloped edges in median optical view.
         (a). With 6 narrow longitudinal furrows (Fig. 19-b) not reaching to the poles; mean average diameter 29 microns. *Eschscholtzia**
         (b). Without narrow longitudinal furrows; mean average diameter 24 microns. *Populus*

REFERENCES

[1]Kerner, Anton, and Oliver, F. W.: The Natural History of Plants, 1893, iii, 95.
[2]Koessler, K. K. and Durham, O. C.: A System for Intensive Pollen Survey, J. A. M. A., 1926, lxxxvi, 1204.
[3]Le Maout, Emm., and Decaisne, Jh.: Traite Generale de Bontanique, 1868, 47.
[4]Pope, Maxy Alice: Pollen Morphology as an Index to Plant Relationship, Bot. Gaz., 1925, lxxx, 63.
[5]Scheppegrell, Wm.: Hay Fever and Asthma. Philadelphia and New York, 1922, Lea and Febiger.
[6]Wodehouse, R. P.: Morphology of Pollen Grains in Relation to Plant Classification, Jour. N. Y. Bot. Gard., 1926, xxvii, 145.

TREATMENT OF ASTHMATIC PATIENTS AFFECTED BY PROTEIN OF THE EPIDERMAL GROUP*

By Zella White Stewart, M.D., Iowa City, Iowa

THIS report contains the results of a careful study of a group of 202 cases. How generally they can be applied is not considered. The conclusions may be summarized as follows:

1. That a diagnosis has been made in every case of asthma by testing repeatedly and thoroughly.

2. That a majority of the cases of asthma in this group are sensitive to feathers.

3. That many asthmatics are sensitive to very slight contacts.

4. That specific desensitization has not brought about permanent results in many cases.

5. That absolute relief can be secured when all offending proteins have been found, and the proper evaluation assigned to each as to the extent it is entering into the case as a causative factor, and all such eliminated from the food and surroundings.

I have tested in all 202 cases prior to May 1, 1926. All of these were clinically cases of allergy and all have given positive skin reactions. During this same period I have made complete tests in six cases that clinically were not cases of allergy. This was done in order to rule out sensitivity. They were clinically cases of sinus infection, chronic bronchitis, dermatitis, digestive disturbance and frequent colds.

The following case will illustrate some of the difficulties met in many cases in securing positive skin reactions:

Mrs. H. C., aged 42, was first seen in July, 1922. She gave a history of hay fever as a child and asthma since 18 years of age. At this time she was never free from marked asthmatic bronchitis, wheezing and shortness of breath on exertion and had frequent severe attacks of asthma. Her condition was complicated by exophthalmic goiter. Due to the malnutrition accompanying the same her skin was dry and unhealthy.

During 1922 she was tested three different times with all available proteins by the scratch tests without results. She spent the winter of 1922-23 in Arizona hoping her bronchitis would improve in a milder climate so that she could submit to an operation. Her asthma was worse on her journey south and during her stay there she was confined to a hospital. Her chances of contacts with proteins in a hospital were limited to feathers, wool, powder and foods.

In the summer of 1924 she was operated on for goiter. The report from the hospital in regard to her asthma was as follows: "It seems to us that rather than being a foreign protein affair, it is more of an asthmatic bronchitis, as most of her asthmatic attacks

*Read before the American Association for the Study of Allergy, Washington, D. C., May 17, 1927.

come from a severe and prolonged cough and seem definitely associated with bronchitis. The prognosis for cure we do not feel is good as her bronchitis is firmly established."

Six months after the operation her general condition had greatly improved, she had gained in weight, her skin was in healthier condition. Her asthma remained the same. She was retested by the scratch method with the complete list of proteins, with no results. I then tested her by the intradermal method and obtained reactions to feathers and orris root and questionable reactions to rabbit hair, muskrat fur and sheep's wool. With the elimination of these proteins she has had months free from every symptom. Her chronic bronchitis has cleared up entirely.

Her last two attacks were definitely traced to contact with furs. She is still under supervision and being desensitized to orris root, as this seems to be the one protein she is unable to avoid entirely. Three years ago her weight was 100 pounds. It is now 150 pounds.

Diagnosis was made in this case after repeated tests made during a period of four years.

Of the 202 cases 19 or about 10 per cent gave no definite reactions after a complete testing of all proteins by the scratch method, and in several cases the most important proteins had been tested repeatedly. All of these cases gave definite positive reactions by the intradermal method. In a few cases false reactions were obtained to proteins which in the clinical study of the case were found not to be an etiologic factor.

I found this true not only with the intradermal test but to a lesser degree with the scratch test, and especially do I find this true in testing with the proteins of the food group. Usually they are foods taken infrequently and in small quantities, which may account for their not being clinically etiologic factors.

I believe the intradermal test is most valuable and is without danger if the patient's sensitivity has first been determined by the scratch method. I have several cases showing marked reactions to the scratch tests. In these the intradermal test would be dangerous.

Of the 90 per cent who gave positive skin reactions during the first tests or repeated testing, eight cases or about 5 per cent did not clear up entirely; that is they were not free from light attacks of wheezing, shortness of breath on exertion and symptoms of bronchitis until minor causes had been discovered by the intradermal test.

Of this group of 202 cases showing 100 per cent positive reactions 116 belong to the epidermal group, the other 86 were food or pollen cases only.

An analysis of this group of 116 epidermal cases indicates that feather proteins are the most important in the etiology of asthma. Thirty-three or 28 per cent were due to feathers only. A number of these cases gave + – reaction to one or two foods which proved to be of no consequence. In another group of 37 cases feathers were the primary cause, secondary reactions were to animal hairs, foods or pollens and in many of these proteins classed as secondary were found to have little etiologic value.

The size of the reaction is not a criterion as to its etiologic importance for this can only be determined by personal inspection of the patient's surroundings at home and at work as to contacts.

Feathers have proved to be the only cause or the primary cause of 70 cases or 60 per cent of this group of 116 epidermal cases. Another 22 cases

or 16 per cent show feathers to be secondary causes. In this group feathers gave + or + + positive reaction and clinically no case was relieved from all symptoms until they were eliminated.

Animal hairs have been the cause alone in only 5 cases or 4 per cent; they have been the primary cause in 23 cases or 20 per cent. Foods have been the primary cause in 7 cases with epidermals as secondary causes and secondary factors in 16 cases. Various pollens have been primary with epidermal as secondary in 10 and secondary factors in 12 cases.

In this group the high percentage of asthma due to contacts with feathers compared to asthma due to animal hair agree with the clinical study of cases as to their possible contacts. Everyone lives with feathers the year around. Few come in contact with live animals and in most cases contacts with animal hair are traceable to hair used in upholstering and clothing.

The extreme sensitiveness of the majority of patients was shown not necessarily by the size of the reaction, but by symptoms caused by slight contact, makes the education of the patient as to the need of avoiding contacts most important. The following case illustrates this sensitiveness:

Dr. W., aged 35, has had asthma since childhood. He lived on a farm until he went to medical college. He was seldom free from symptoms while on the farm but could go to his brother's home in a small town three miles away and be fairly comfortable.

He spent seven years in college and remained practically free except for his visits home. He started practicing in a city in Iowa doing mostly office work. He remained free until he was married four years ago. Since then he had trouble constantly with severe attacks in cold weather. His reactions were goose feathers + + + +, duck feathers + +, chicken feathers +, corn pollen + + + +. These reactions fit in with his history. On the farm they raised geese and had feather beds as well as pillows. They used corn the year around, feeding the cattle and using the corn cobs for the fire. His contacts were of daily occurrence.

His brother's home was new and was free from corn, and feather beds, although they had feather pillows. His seven years in college were spent in a large city. The hours spent in his room were a small part of the twenty-four and besides his pillow probably was of chicken or duck feathers to which he was not very sensitive. When he was married his mother sent him six goose feather pillows, and his asthma returned. The feathers were removed from the house, and the house thoroughly cleaned to eliminate any feather dust where it might be in rugs, curtains and bedding. All signs of asthma immediately disappeared. At the end of two months he had gained 15 pounds. Later he reported that during zero weather they had used an extra quilt which had been stored away since the preceding winter. Before morning he began to wheeze and choked up. At the end of forty-eight hours all symptoms of the attack had disappeared.

The following case shows failure to obtain entire relief due to slight contact.

Ellen M., aged 7 years, had asthma since 2 years of age. Reactions to rabbit hair + + + +, chicken feathers + +. She lived on a farm, the chicken yard was located near the home. There were no asthmatic attacks after the removal of furs and all feathers from the house, but her bronchitis persisted and was made worse by every wind and storm. Her general health did not improve. This condition remained the same for two years. I then sent her to a tubercular sanatorium for consultation. The report stated there was no evidence of tubercular involvement but evident enlargement of the bronchial tubes.

It had been noticed that if the snow was on the ground for two or three weeks at a time Ellen's bronchitis would clear up entirely and she would gain physically. I then had

her leave the farm staying for two months in a home free from feathers and furs. Attempt was made to drain the dilated bronchial tubes by having her virtually stand on her head for five minutes three times daily.

They sold the chickens on the farm, plowed up the ground and seeded the same before Ellen's return home.

She has been perfectly well for over a year, has not missed one day of school, has not had a cold, has changed from a poorly nourished, listless child to one in perfect health and full of energy.

Another case.

Mrs. H. showed multiple reactions, among them sheep's wool. I had close supervision of her case for four years and finally obtained absolute relief when all wool rugs were removed from her home.

Desensitization.—No attempt is made for specific desensitization until all symptoms have cleared up following either the thorough removal of all offending proteins from the surroundings or the removal of the patient. This is a clinical test of the value of the reactions. Size of the wheal is no indication for treatment. Reactions are only symptoms and if no contacts can be found may be disregarded except as a warning to avoid the same. Many reactions can finally be ignored but not until a thorough investigation has been made to determine which ones are active factors. This means a most careful inspection of a patient's home and surroundings. Specific desensitization is undertaken for proteins where there is unavoidable or casual contact. I seldom attempt to desensitize for horses, dogs, cats, other pets or furs. It is much more effective to get rid of the animals or furniture. In cases where it is impossible to eliminate contacts with animals such as on a farm I have been able to obtain relief but not such good results as have been reported by others. Several cases have been treated for horse hair over long periods increasing the doses to 1:500 and several to 1:100 dilutions. They show little if any decrease in their sensitiveness on exposure. I have close supervision of my cases for two years or until they have gone one year free of symptoms. The knowledge they gain during this time of the slight contacts causing return of their symptoms and of the means of avoiding the same is more important than the results they have received from treatment.

The following cases could be duplicated many times among the two groups, those who have been desensitized and those who have not but who have been under close supervision for at least two years.

Professor G.—Asthma since childhood, reaction to feathers and marigold. After elimination of these proteins he was desensitized to feathers working up to 1:100 dilution and continued this over one year. He has no possible contacts in his home or surroundings and has been free from attacks for four years except if he travels by pullman. If he takes his own pillow, and leaves the train early in the morning he is all right, but if he remains while the porter makes up the berths, he will have an attack within 36 hours. It is a short attack and not severe, usually in 2 days it is gone. One would expect that his treatment had decreased his sensitivity. He states that he has never been so well, never has colds, but he is afraid to travel or visit with relatives.

Mr. L. has had asthma for years. His only reactions are to feathers. He has had two years' continuous treatment and has been absolutely free from asthma or even a cough. He drove into his garage one night and decided he would kill the numerous sparrows in-

habiting the same. After his efforts he spent most of the night struggling for his breath. He can travel and stay at hotels if the pillows are removed but he cannot spend a night at the home of his mother-in-law, which is an old house with many feather beds.

In many patients who have not been desensitized but have had two years' supervision and have learned what contacts to avoid, the results are as good.

To secure results with pollen the necessity of several years of treatment is well established. Better results might be obtained if the same procedure were carried out in the case of animal emanations.

Better results are obtained with men than with women where the trouble is due to animal emanations found in homes on account of less opportunity of contact to small amounts of protein left in curtains and rugs even after everything has been removed.

Perhaps years of freedom with the accompanying improvement in general health will decrease this sensitiveness. This I think will occur especially in children.

Even if desensitization does not accomplish all that could be wished for, I am thoroughly convinced that every asthmatic, regardless of the duration of the trouble, can be absolutely relieved when all offending proteins have been discovered. It may take months of testing and retesting and the use of both scratch and intradermal method. It will mean close inspection of surroundings and supervision for a long period.

END-RESULTS

Of this group of 116 cases where the primary cause has been due to animal emanations, 67 or 58 per cent have been free from all symptoms for at least one year. This has been due to the thorough eliminations of the offending proteins and to the knowledge they have acquired of their individual sensitiveness to contacts. Many of these have been desensitized to one or more proteins. Close supervision and observation of these cases indicates that freedom from contacts has brought about these results. This group has not only been free of symptoms, but has shown improvement in general health and freedom from colds.

Twenty-two cases or 19 per cent have had about 75 per cent improvement. They do not have asthmatic attacks but still show protein irritation by wheezing, shortness of breath on exertion and by frequent colds and bronchitis. Many of these cases are free from all symptoms for several months. They are still under supervision and many of them are having their tests checked over.

Three cases or 2 per cent have had no improvement. They have been under treatment for two years and have given satisfactory reactions, but their condition is proof that all factors have not been discovered or all contacts found.

Three cases or 2 per cent have been discharged for the reason that it was impossible to get their cooperation in eliminating the causes of their trouble.

Eleven cases or 9 per cent discontinued treatment or supervision after complete tests were made. They report freedom from attacks but slight symptoms of irritation. They are satisfied with the results.

Five cases or 4 per cent discontinued treatment and have had no improvement. This in some cases was due to the advice of their physicians who remarked that the work in allergy was still in an experimental stage.

In five cases or 4 per cent I have no knowledge of their present condition.

I keep all my cases under supervision for at least two years, if possible or until they have gone free of trouble for one year. Usually the first year they report weekly, either in person or by letter, whether they are receiving desensitization or not, and the second year monthly. By the time they have gone one year free from symptoms they have acquired the knowledge of what they must avoid.

STUDIES IN ASTHMA*

I. A CLINICAL SURVEY OF 1074 PATIENTS WITH ASTHMA FOLLOWED FOR TWO YEARS

By Francis M. Rackemann, M.D.,† Boston

As a preliminary to a more intensive study of asthma, an attempt has been made to follow all those patients seen at the Massachusetts General Hospital and in private practice, whose first visit was prior to January 1, 1925, and in whom, therefore, the follow-up note would cover a period of at least two years.

The object is twofold: first, to study the clinical classification of the patients, partly to compare this present grouping with previous classifications and partly to see whether the preliminary classification would be confirmed by subsequent observations of the patients. The second object is to study the results of treatment and any light which these results of treatment or clinical management might throw upon the mechanism of the asthma.

The total series comprises 1514 patients. Of these, 1074 patients (70 per cent) have been either heard from or seen again between January 1, 1927, and May 1, 1927, and the end-results thus obtained are presented herewith.

This series of 1074 cases has been divided into three general groups: extrinsic, intrinsic and unclassified asthma. A brief description of terms and methods of diagnosis is necessary. "Extrinsic" is the term applied to those cases hypersensitive to some foreign substance outside of the body, and who have athma on exposure to, or contact with it. The term "intrinsic" implies that the essential cause of the trouble is inside of the body. The miscellaneous "unclassified" group includes the cases with unknown cause. Each of these main groups has been divided into subclassifications. Similar classifications of the types of asthma have been made previously by the author,[1] by Cooke,[2] and by others,[3] partly on the basis of the causative agent and partly on the basis of the end-results of treatment. These classifications are always unsatisfactory in some degree, but are necessary for any approach to the study of the mass of data which accumulates.

The diagnosis of the cause of asthma and the classification of the particular case must continue to rest chiefly on the history of the disease in the particular patient and to be dependent upon the circumstances under which the attacks of asthma have occurred. Thus if the asthma was entirely relieved when the patient moved from one environment to another, such a move clearly suggests an extrinsic factor, probably in some dust which was causing the attacks in the first place, and from which the patient escaped by the move.

*The expenses of this investigation were met by an anonymous donation known as the "M. G. H. Asthma Fund."

†From the Medical Services and Anaphylaxis Clinic of the Massachusetts General Hospital.

Read before the American Association for the Study of Allergy at Washington, D. C., on May 23, 1927.

Skin tests by the scratch method and by the intradermal method, and frequently by both at the same time, have been useful in two ways: first, to confirm the diagnosis as suggested by the history, and second, to point out other possibilities, which, however, must always await confirmation by further cross-examination of the patient's story, or perhaps by such a clinical experiment as a change in residence, a restriction of diet or an elimination of some supposedly offending substance.

In case the results of the skin tests cannot be confirmed in this way, the suspected substances have been disregarded as a cause of the present trouble and considered simply, with Cooke, as "potential" causes of asthma. In other cases with a positive history, but with negative tests, the diagnosis has been based upon this history and not excluded because the skin tests were negative.

The results of treatment made available by the follow-up system have provided another means of confirming the diagnosis and classification. Methods of treatment have been selected according to the probable cause of asthma, as determined by the preliminary study. Thus in the extrinsic group, the offending foreign substance has been eliminated, perhaps by removing some one article like the cat, the feather pillow or a substance met with in the occupation or perhaps by a more radical procedure, like a change in climate, residence or work. In case the offending substance could not be eliminated, attempts to "desensitize" the patient to it have been made.

TABLE I

1074 CASES OF ASTHMA

GROSS CLASSIFICATION

DECADE OF ONSET	0-9	10-19	20-29	30-39	40-49	50-59	60-	TOTAL
Extrinsic Asthma	162	75	96	55	27	9	1	425
Intrinsic Asthma	128	59	78	97	75	43	19	499
Miscellaneous Unclassified Asthma	23	32	28	31	27	7	2	150
Total	313	166	202	183	129	59	22	1074

In the intrinsic group, treatment has consisted of removing foci of infection and in improving the general condition of the patient by changes in dietary, by regulation of rest and exercise and by removal of those factors which might cause irritation to mind and body. In fact, this attention to "general hygiene" has always been a very important feature of the treatment. In the cases of bacterial asthma and in many others where repeated respiratory infections have been important as primary or as secondary causes of asthma, vaccines, both stock and autogenous, have been employed to produce an immunity by specific or nonspecific means.

Table I shows the numbers of cases in each main group, arranged according to the decade of onset of the asthma. As originally pointed out by Walker,[3] the percentage of extrinsic asthma, which is high among children, bears a constantly diminishing relation in the older decades to the cases of intrinsic asthma and to the total series. Though Table I does not give the figures, males and females occur about equally throughout the series, except that among those with an early onset of asthma, males predominate.

Extrinsic asthma is the easiest group to study. Chart I shows a dot for each patient, still under treatment, plotted opposite his present age, shown by the vertical figures at the left, and placed in the proper decade of onset of his asthma, according to the horizontal figures at the bottom. The circles represent those patients asthma-free for at least two years* and the crosses represent deaths, whether from asthma or from any other cause. Chart I shows a definite grouping of present young people, whose asthma began in childhood; and here the number of circles is of particular interest. It is

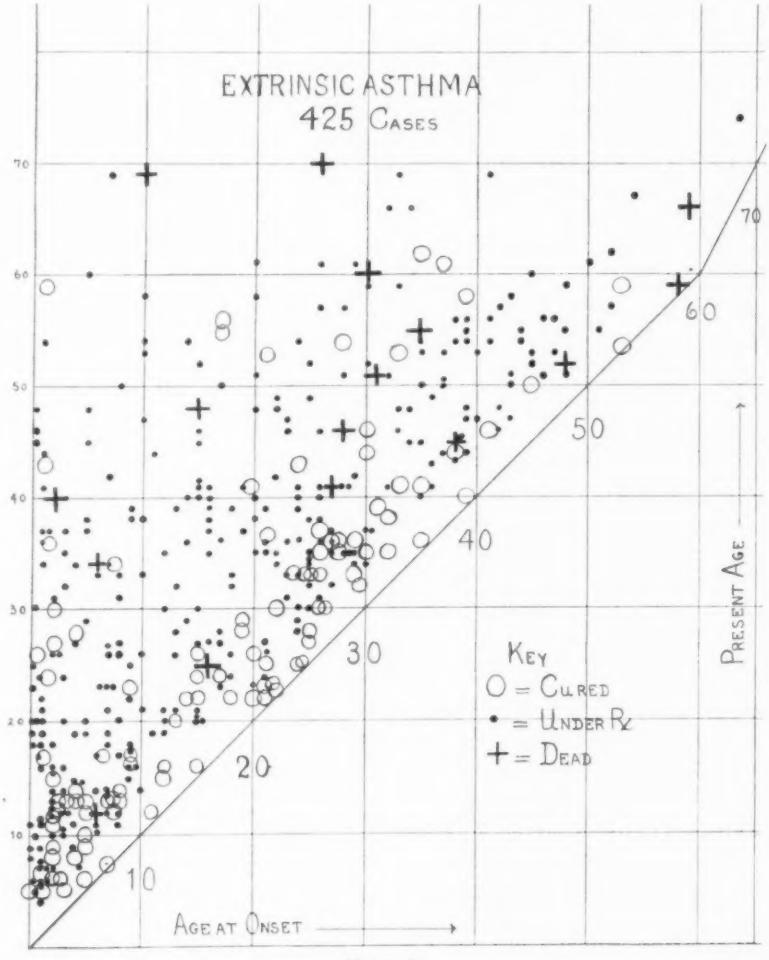


Chart I.

worthy of note that asthma of the extrinsic type rarely begins after the age of 45. (Compare Chart II later.)

The subclassification of these extrinsic cases is shown by Table II. Here we have groups of cases with the end-results as obtained by the follow-up questionnaire. The sex incidence, the percentage of positive family histories and the total number of positive skin reactions are also included.

*Later in this paper the word "cured" in quotation marks is used to denote patients asthma-free for two years or more without treatment. The author fully appreciates the danger of using such a word and agrees with the comments recently made by M. H. Kahn[4].

Table II shows asthma due to pollens, due to animal dusts and due to unidentified causes. The patients with "pollen asthma" include only those who come without particular reference to their hay fever. Obviously, however, true pollen asthma can only be an aggravation of hay fever, and if it is true that one-third of all patients with hay fever wheeze during the pollen season and therefore have asthma, as Rackemann[3] pointed out, the present figure is far too low.

TABLE II

EXTRINSIC ASTHMA

CLASSIFICATION AND RESULTS

	"CURED"	IMPROVED	SAME	DEAD	TOTAL	FEMALE	PER CENT POSITIVE FAMILY HISTORY	POSITIVE SKIN TESTS
Pollen asthma	13	44	8	5	70	31	45%	68
Pollen asthma infected	5	23	10	1	39	23	40%	35
Summer asthma, negative tests	10	10	10	2	32	15	10%	0
Animal asthma	22	32	5	1	60	32	60%	60
Animal asthma, infected	0	11	2	0	13	6	61%	13
Extrinsic mixed and unidentified	22	80	13	6	121	64	45%	121
Mixed and unidentified with negative tests	18	14	5	0	37	16	48%	0
Extrinsic specials*	17	26	9	1	53	20	54%	52
Total	107	240	62	16	425	207	47%	349
Per cent of total	25%	56%	15%	4%	100%	49%	47%	82%

*These include:
Dust—Feathers 10, orris 3, cotton dust 1, hops and malt 1, fish glue 1, dyes 1, Formalin 1, wheat (as dust) 5.
Foods—Eggs 12, wheat 4, fish 3, milk 2, mixtures 9.

The poor results of treatment in eight cases of the simple type and in ten cases of the infected type represent the difficulties of treatment and indicate also that the presence of infection is a severe obstacle to treatment. The fact that the total number of positive skin tests in the two groups falls short of the total number of patients by six is because skin tests were not done. But these six cases have been included here, rather than in the next group, simply because the story of asthma occurring only during the ragweed season was so definite.

A group of 32 cases is designated "summer asthma with negative tests." Here the cause of trouble is unidentified, except in so far as the history shows the occurrence of asthma only in well-defined seasons, which for each case remain quite the same from year to year. In spite of skin tests, by the scratch method and the intradermal method, as well as by direct application of what appeared to be the offending pollen, to the conjunctival sac, it has been, so far, quite impossible to prove that pollens are the cause. Moreover, the results of treating these patients, either with strong pollen extracts or with vaccines, have been quite unsatisfactory. Meantime, nevertheless, ten patients are "cured." Six of these were children who became asthma-free without particular treatment other than directions for improving the general hygiene; one of the adults had vaccines; another has moved to California and the two others have become symptom-free without knowing why.

The low percentage of positive family history in this group of summer asthma is interesting, particularly as the contrast with other extrinsic groups is so great.

The group of "animal asthma" shows a better percentage of good results than any other. Among the improved cases there are a great many patients who claim to have been "cured" of their asthma, but who have not been relieved of symptoms long enough to be definitely counted in the "cured" group. It is of interest to note, in connection with the cases of simple animal asthma, that many patients are free from asthma so long as they keep away from the offending animal, but as it is entirely beyond their control to keep animals from all the places which they frequent, they still have symptoms whenever they cannot avoid the particular contact. In the majority of cases, contact can be avoided for most of the time, and the slight change in environment is easier and more certain of results than any direct treatment. The few cases still unimproved are those who have been unable to make the necessary changes to escape from the offending substance and whose specific treatment has been unsuccessful.

In the group of patients whose asthma is due to unidentified causes the number is large. The diagnosis has been applied chiefly to those whose story shows a clear relationship between their asthma and their environment. Many of them have other evidences of hypersensitiveness, like eczema or hay fever; most of them give skin reactions to house dusts and frequently to other substances at the same time. The term "mixed and unidentified" must suffice for the present.

Table II includes a second group of cases whose skin tests were quite negative, but whose stories were so definite as to preclude a cause of asthma other than some obscure extrinsic factor. For example:

A woman of about 45 had had asthma since the age of 20. Her father had had hay fever. Her attacks had occurred at all seasons of the year and she had lived all her life in the same house in Belmont. Since her skin tests were repeatedly negative, and since the story was of trouble which was so persistent, she was at first classified as "bacterial asthma" in the intrinsic group. But treatment was of little benefit. Recently she wrote that for two years she had remained practically free of all trouble from her asthma, and luckily, she added this note: "Please note that two years ago I moved from Belmont to Brookline." This note, of course, has changed her classification, and she is now placed in the extrinsic group among those cases of "mixed and unidentified asthma, with negative tests."

The 37 cases listed as mixed and unidentified, with negative tests, are all of this type. The fact that in five cases the asthma is still unimproved, is explained, in one instance, by the patient going to Italy and having no further asthma, but on return having trouble again; in the second instance, by a marked improvement on moving to California, but with a recent return of asthma out there; in the third instance, by the fact that the asthma, which at first was associated only with a farm barn, is now not limited to such exposure and is much more chronic; in the fourth instance, by the onset being shortly after moving to a farm, persisting while there, but with comparative freedom from symptoms when in cities; and in the fifth instance, by the fact that, although the patient was temporarily improved by injections

of feather extract (to which he gave a slight skin reaction) he is entirely free on various occasions, one of them being when he was in the hospital ward. In this unidentified group, with negative tests, it should be noted that the incidence of a positive family history is close to the average percentage.

The group designated "extrinsic specials" includes a number of patients in which the cause was well defined and different from any of the other groups. The rather small number of cases, in which the asthma was due to such things as feathers and orris powder, is surprising in view of so many enthusiastic reports in the literature which give the impression that these substances are quite common as causes of asthma. The many young girls who develop a sensitiveness to orris powder manifest this by vasomotor rhinitis and not by asthma in most cases.

Of the total, 53 cases, under this heading, it is interesting that foods produce asthma in 30 cases. All of these are in small children except for 8 adults, each of whom is of special interest. Two were college students, so sensitive to eggs as to find it necessary to avoid all cake and puddings in their dietary. Another was a young surgeon, so sensitive to fish and fish glue that he could not lick a postage stamp without swelling of his tongue and mouth. He also had asthma from the dust of dried fish glue. The fourth, a storekeeper, was sensitive to fish and eggs. Two women were sensitive to fish, and one of them was also sensitive to a great variety of other foods, the most common of which were orange, apple and celery. The other two patients, a man and woman, were sensitive to wheat as a food. All of these recognized their sensitiveness to certain foods before the test and all were free of symptoms so long as they avoided the offending articles.

TABLE III

INTRINSIC ASTHMA
CLASSIFICATION AND RESULTS

	"CURED"	IMPROVED	SAME	DEAD	TOTAL	FEMALE	PER CENT POSITIVE FAMILY HISTORY	POSITIVE SKIN TESTS
Bacterial asthma	25	128	42	7	202	98	36%	44
Bacterial asthma in children	34	49	5	2	90	24	48%	18
Reflex asthma, not N. & T.	18	35	11	2	66	41	33%	10
Reflex asthma, N. & T. only	10	20	7	3	40	22	43%	2
Cardiac asthma	1	13	10	21	45	20	40%	7
Bronchitis and emphysema	3	14	29	10	56	18	21%	3
Total	91	259	104	45	499	223	37%	84
Per cent of total	18%	52%	21%	9%	100%	45%	37%	17%

One case with negative tests was included in this group. He was a child of two who developed asthma and urticaria on every attempt to take cow's milk or goat's milk. At one time another doctor did find a slight reaction to the albumen in cow's milk. This child is now six years old and is still

unable to take milk in any form. Unfortunately no recent tests have been made.

Intrinsic asthma is the term applied to the cases where the cause is inside the body. (Chart II for intrinsic asthma corresponds in every way to Chart I for extrinsic asthma.) The author feels that such a diagnosis is correct in several fairly definite groups of cases and that the use of the term need not in any sense be forced simply because of the inability to identify an extrinsic

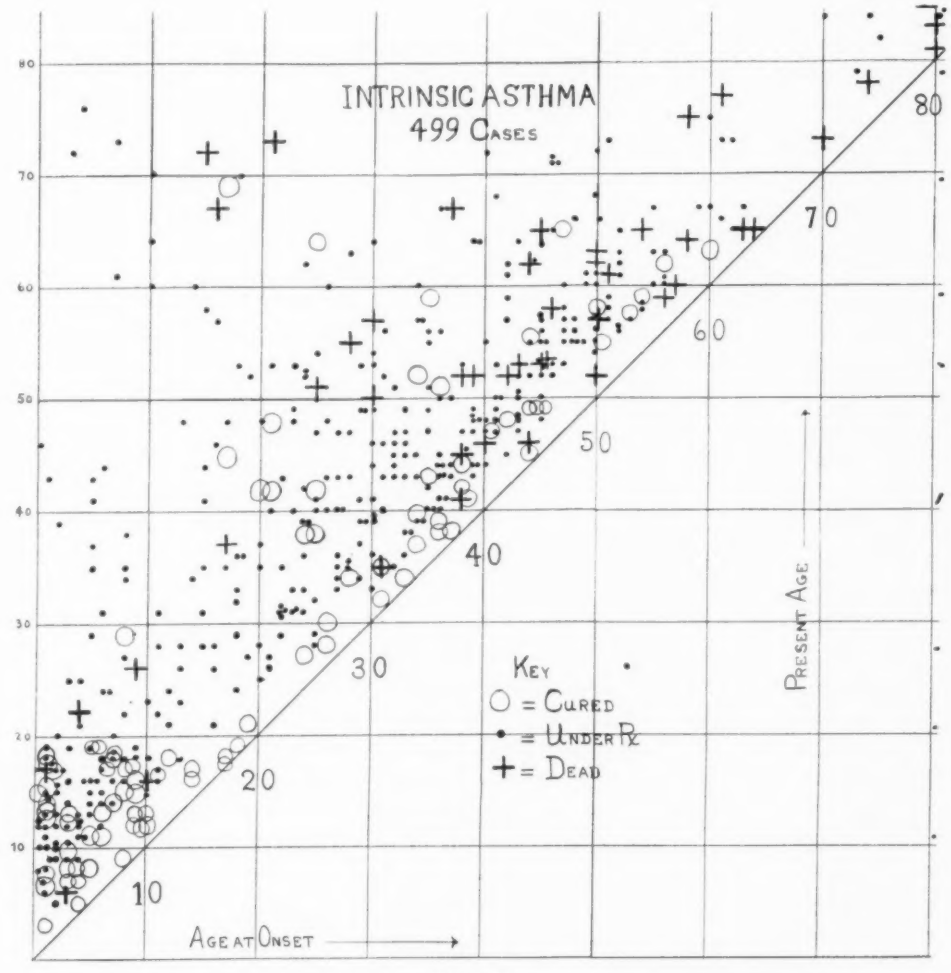


Chart II.

cause. The intrinsic group includes various subclassifications, as shown by Table III.

"Bacterial asthma" applies to those cases whose asthma is apparently dependent upon an infection in the upper or lower respiratory tract. "Reflex asthma" indicates that the cause of trouble is either outside of the respiratory tract entirely, as in bad teeth, cholecystitis or constipation, or

that, if inside of the respiratory tract, the lesion is well defined, as in an infected sinus or in infected tonsils.

The group of bacterial asthma is of particular interest. Here is a considerable group of patients whose asthma occurs only after some acute respiratory infection including common colds; and this occurrence may happen at very long intervals, perhaps only twice a year, the important point being that the patient is living in the same environment with the same occupation and on the same general diet at all times; facts which would seem to exclude an exposure to any new foreign substance as a cause of the attack. In other cases the evidence of the initial cold is less definite, but again, the intervals between the attacks are long, each one runs a limited course and dependence upon some respiratory infection seems obvious. Individuals with this type of asthma are perfectly well between attacks and show no abnormalities in the chest either on physical examination or by x-ray. Study of the conditions in the nose and throat is in progress.

"Winter asthma" has been used in the past as a convenient term to define an artificial group of these bacterial cases whose trouble begins with the first cold of autumn and persists, with ups and downs, till the warm weather of spring.

The separation from the main group of "bacterial asthma in children" is obviously artificial and is made largely to demonstrate the considerable number of children who have been asthma-free for two years and another considerable number who are improved. Attention should be called to the figure of only twenty-four females in this group of ninety children. In both groups of bacterial asthma are positive skin tests, and yet the diagnosis has been made in spite of this finding. Many of these patients react to house dust and a few of them to such other substances as feathers, dog hair, goat hair, orris powder, etc., but these tests were, with a few exceptions, never well marked, and all except 22 were obtained by the intradermal method, which, in our hands, gives confusing readings in many cases. The real reason to exclude these tests, however, depends upon the fact that in none of these patients was it possible to show that the attacks of asthma were dependent upon exposure to the particular substance. On the other hand, it was perfectly reasonable and logical to explain the attacks on the basis of a respiratory infection. These positive skin tests may well represent a general characteristic of the asthmatic patient rather than a hypersensitiveness which is clinically important.

The designation "reflex asthma" is applied to those cases who have a focus of infection, which may be in the nose and throat or elsewhere, such as in the teeth or in the gastrointestinal tract, and which, because of improvement following treatment can be regarded as a direct cause of asthma. Included in this group are patients with obesity and other general disturbances, which seem to have a very definite bearing on the cause of the trouble; moreover, the study of end-results has clearly justified such a classification. For example: six cases of asthma and obesity seemed to be better of their asthma when their weight was reduced; but whether this can be interpreted as cause and effect is perhaps doubtful.

Analysis of 66 cases in which the cause of asthma appears to be a "reflex" from disturbances outside of the nose and throat, shows, in addition to the six cases of obesity, thirteen cases in which teeth were important, in eight cases the gastrointestinal tract, in four cases "nerves," in three cases syphilis, in one case pregnancy and finally in thirty-one cases the cause of asthma is designated simply as poor hygiene. Poor hygiene includes such items as a poor or unwise dietary schedule, a lack of proper fresh air and exercise, an insufficient intake of fluids, overexertion and continued nervous strain without proper rest periods (or even simply continued loss of sleep, not accompanied by exertion and nervous strain), constipation or indigestion caused by indiscretions in diet, all of which have been relieved by following the simplest directions for general hygiene, which have been the only treatment and have produced rather amazing results in the majority of cases.

In this group of reflex asthma, eleven patients are unimproved, but in spite of that they are here included because the treatment recommended to relieve the particular trouble, which seemed so clearly the cause of the asthma, was not carried out. Thus four obese patients lost much of their asthma when they lost weight, but, when they regained weight, asthma returned.

Of the forty patients with "reflex asthma due to nose and throat pathology," thirty-eight had a focus of infection in the sinuses, nine in the tonsils, and six had a vasomotor rhinitis. Forty-six previous operations were done on these patients (only two of which were tonsillectomies). After examination here, further operations were advised on thirty-two patients, and eight of these had more than one operation (five being tonsillectomies). The other eight patients had less radical local treatment, such as cautery or irrigation, but without surgical intervention. That the designation "reflex" is justified is shown by the results, since of the forty patients ten have become asthma-free and twenty are improved. The seven patients included in the group, but who are now unimproved, did experience temporary relief after operation; but all of them have chronic and extensive sinusitis at the present time.

The diagnosis of "cardiac asthma" has been made in those patients whose asthma bore an unusual relation to exertion and who gave a rather characteristic story of good nights, without being awakened by the nocturnal paroxysm, so typical of other types of asthma. In addition, the group includes those who present some definite abnormality in the size and action of the heart as well as those whose blood pressure is constantly elevated. In this series, however, we have not seen the sudden seizure of dyspnea associated with struggling and excitement which Pratt[6] has so graphically described as characteristic of cardiac asthma. The many patients who have died and the great number whose asthma is unimproved confirm the impression of cardiac damage.

"Chronic bronchitis and emphysema" is the designation of another group which is closely related to the group of cardiac asthma. The distinguishing feature lies in the evidences of faulty oxygen absorption, as shown by chronic cyanosis of the lips and fingers, and of severe and persistent asthma as shown by a barrel-shaped chest in many cases and by markedly high pitched breathing with diminished intensity in all of the cases. The presence of chronic

bronchitis, with cough as an important symptom and with sputum which is considerable in amount and thick yellow in quality, also distinguishes the group. Here too the number of deaths and poor results are both large.

Miscellaneous unclassified cases are included in Table IV. It is gratifying to find that there are only 150 cases in the group. Included under the heading, however, are three special groups worthy of comment. The term "chronic severe asthma" is purely artificial, but is applied to a characteristic type of patient seen not infrequently in the wards of the hospital. Such a patient is most often a man, with an onset of his asthma in the thirties or before, who has had asthma usually for three to five years, rarely for ten or fifteen years, and frequently dates the onset from the time of a severe nervous strain, com-

TABLE IV

MISCELLANEOUS UNCLASSIFIED ASTHMA AND SPECIAL GROUPS

	"CURED"	IMPROVED	SAME	DEAD	TOTAL	FEMALE	PER CENT POSITIVE FAMILY HISTORY	PER CENT POSITIVE SKIN TESTS
Miscellaneous unclassified	15	40	34	16	105	56	35%	34
Special Groups								
Chronic severe asthma	0	2	15	5	22	6	36%	5
Fatal asthma	0	0	0	10	10	10	50%	5
Asthma and tuberculosis	0	3	1	9	13	4	56%	5
Total	15	45	50	40	150	76	38%	49
Per cent of total	10%	30%	33%	27%	100%	51%	38%	39%

monly in the war. The asthma in these men is of maximum severity, requiring doses of adrenalin every two or three hours; it is not relieved by a stay in the ward, nor is it much changed on returning home. These patients are always thin and pale, they sweat easily, cannot eat, are restless and very uncomfortable. Physical examination frequently shows sinusitis of extensive type. The lungs are emphysematous and the heart action is rapid, with low blood pressure, but the abdominal organs and urine are normal, and the blood calcium, blood nitrogen and blood sugar are within normal limits. Skin tests are almost always negative. Treatment of these poor unfortunates is most unsatisfactory. While the temptation to regard them as having "nervous asthma" is great, yet attempts to relieve them by psychic treatment have been unavailing.

The second special group is "fatal asthma," which has previously been described by Rackemann[7] as occurring among middle aged women who tend to slight obesity and whose asthma has occurred largely in definite attacks, but eventually has led to more severe attacks, the last of which was fatal. So far ten cases have been collected.

"Asthma and tuberculosis" have been associated in thirteen patients, most of whom had tuberculosis in an advanced stage, and have died of it. The association of the two diseases is interesting because the incidence of asthma among large groups of tuberculous patients is considered to be small. The patients here had asthma which was often severe, but only in three of the cases was it possible to demonstrate any relation between the severity of the

asthma and the activity of the tuberculous infection. No claim for an etiologic relationship is made. Five of the patients tested had positive skin tests, and only one of these was improved by the treatment indicated by the tests.

Table V shows the gross results of treatment in the entire series. Twenty per cent of all the cases have remained free of asthma for at least two years since their last treatment. These 213 "cured" cases will be the subject of a special study to follow. On the other hand, another 20 per cent have remained quite unrelieved of their trouble and 10 per cent have died from various causes. The incidence of death seems to be a rather high figure. In only twenty-one of the cases was the death directly due to asthma, for in thirteen it was due to acute respiratory infections, in twenty-one to cardiac conditions, in nine to tuberculosis, and in the remainder to various other conditions, for the most part organic, with two violent deaths, and nineteen concerning whom we have no information further than that the patient is no longer living.

In the entire series of 1074 cases shown in Table V, males are rather more numerous than females, but the difference is not striking. A positive family history was obtained in 42 per cent of all the cases. While at least 45 per cent

TABLE V

1074 CASES OF ASTHMA FROM RESULTS

	"CURED"	IMPROVED	SAME	DEAD	TOTAL	FEMALE	PER CENT POSITIVE FAMILY HISTORY	POSITIVE SKIN TESTS
Extrinsic asthma	107	240	62	16	425	207	47%	349
Intrinsic asthma	91	259	104	45	499	223	37%	84
Miscellaneous unclassified asthma	15	45	50	40	150	76	38%	49
Total	213	544	216	101	1074	506	42%	482

of the patients gave positive skin tests, it should be noted that certain cases in the extrinsic group failed to give positive skin tests, while certain cases in other groups did show positive skin reactions that were neglected as an important factor in the cause of the asthma. A study of these irregular skin tests is contemplated.

DISCUSSION

This paper presents briefly the gross results of a study of 1074 patients with asthma, all of whom were seen for the first time at least two years ago, so that the final notes showing the condition of these same patients at the end of two years or more are available for a general survey of their progress.

The two charts showing the decade of onset, the present age and the present status of 425 patients in the extrinsic group and of 499 patients in the intrinsic group, demonstrate clearly the pleomorphic character of asthma as a disease and give further support to the conception that asthma is a symptom based on a variety of causes rather than a disease with a single etiology.

It was hoped that a survey of such magnitude would demonstrate certain natural tendencies of the symptom asthma to come and go and that it would point to a mechanism which might explain the natural history of the disease.

For example, it is interesting to observe the number of children who have remained free of asthma for the past two years or longer. For many of these cases it is possible to give a definite explanation as in the elimination of some extrinsic factor, but in many others such an explanation is not so easy and it may be that these results indicate a natural tendency for asthma in children to disappear spontaneously or, as it is said, "to be outgrown." This particular subject will, however, be discussed in a separate paper.

Beyond this, the study, so far, has added little that is new.

That this classification of patients with asthma represents a reasonably accurate study is shown by Table VI, which gives the number and percentage of patients in each group as determined by the writer on three separate occasions. The figures are cumulative in the sense that many patients in this present classification have been studied previously. No attention, however, has been paid to previous classification of the particular patient whose case

TABLE VI

COMPARISON OF CLINICAL CLASSIFICATIONS OF 1918, 1921 AND 1927

	1918[8]		1921[1]		1927	
CLASSIFICATION	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Extrinsic asthma	42	28%	307	47%	425	40%
Pollen asthma	12	8%	150	23%	70	7%
Pollen asthma, infected	12	8%	28	4%	39	4%
Summer asthma	--	--	18	3%	32	3%
Animal asthma	16	11%	45	7%	60	6%
Animal asthma, infected	--	--	16	3%	13	1%
Mixed and unidentified	--	--	15	2%	121	11%
Mixed, etc., with neg. tests	--	--	--	--	37	3%
Extrinsic specials	2	1%	35	5%	53	5%
Intrinsic asthma	73	49%	272	42%	499	46%
Bacterial asthma	46	31%	121	19%	202	19%
Bacterial in children	--	--	38	6%	90	8%
Reflex asthma, not N. & T.	5	3%	58	9%	66	6%
Reflex asthma, N. & T. only	4	3%	9	1%	40	4%
Cardiac asthma	--	--	--	--	45	4%
Chronic bronchitis and emphysema	18	12%	46	7%	56	5%
Unclassified	35	23%	69	11%	150	14%
Total	150	100%	648	100%	1074	100%

has been summarized and brought up to date "de novo." Never before has a real effort been made to modify the grouping on the basis of end-results.

On the whole the percentages in the three classifications agree fairly well. The percentage of extrinsic asthma is lower in 1927 than it was in 1921 and the other major groups are correspondingly higher. Such a finding, in the face of increasing knowledge and clinical experience, would seem to refute the ideas of many co-workers who strive to show that all cases of asthma depend upon a background of hypersensitiveness to some foreign substance. The lesser changes in the present series are the marked diminution in the proportion of pollen asthma, which is almost made up by the increase in the mixed and unidentified cases in the extrinsic group. The slight decrease in the percentage of several other extrinsic groups depends upon the growing evidence that positive skin tests may not always be of clinical importance. The increase of the unclassified cases is disappointing.

The classification as presented is not perfect because our knowledge of the underlying mechanism is still lacking, but the fact that reclassification of patients in the same clinic yields figures for the different groups which are quite comparable from time to time, indicates that the method is reasonably accurate and clinically useful.

REFERENCES

[1]Rackemann, F. M.: A Clinical Classification of Asthma, Am. Jour. Med. Sc., 1921, clxii, 802.
[2]Cooke, Robert A.: Studies in Specific Hypersensitiveness. New Etiologic Factors in Bronchial Asthma, Jour. Immunol., 1922, vii, 147.
[3]Walker, I. C.: Bronchial Asthma, a Clinical Study of 400 Patients with, Boston Med. and Surg. Jour., 1918, clxxix, 288.
Larson, N. P., and Bell, S. D.: Classification and Management of Asthma in Childhood, Am. Jour. Dis. Child., 1922, xxiv, 441.
Rowe, A. L.: Bronchial Asthma in Children and Young Adults, Am. Jour. Dis. Child., 1926, xxxi, 51.
Menagh, Frank R.: The Results of Treatment in Bronchial Asthma, Ann. Clin. Med., 1927, v, 656.
[4]Kahn, M. H.: Present Status of the Curability of Bronchial Asthma, Arch. Int. Med., 1927, xxxix, 621.
[5]Rackemann, F. M.: The Results of the Specific Treatment of Hay Fever, Jour. Immunol., 1926, xi, 81.
[6]Pratt, Joseph H.: Cardiac Asthma, Jour. Am. Med. Assn., 1926, lxxxvii, 809.
[7]Rackemann, F. M.: Fatal Asthma, Boston Med. and Surg. Jour., 1926, cxciv, 531.
[8]Rackemann, F. M.: A Clinical Study of 150 Cases of Bronchial Asthma, Arch. Int. Med., 1918, xxii, 517.

ESSENTIAL DIFFERENCES IN CHRONIC POLLEN HAY FEVER AND ASTHMA IN CHILDREN AND IN ADULTS*

By I. S. Kahn, M.D., San Antonio, Texas

INTRODUCTION

THE pollens involved in this study were those of the ragweeds, careless weeds, mountain cedar and various grasses. One hundred cases of pollen asthma in children and three hundred cases of pollen asthma in adults comprise the material considered in making deductions. The differences noted in children from the usual manifestations of adult hay fever and asthma were all in cases of combined ragweed and grass sensitiveness. Respiratory system allergic disease of pure animal epithelial emanation, food or orris etiology is rare in my community.

The Actual Asthmatic Attack.—Asthmatic attacks in children are said to differ in no way from those of adults. In my experience, in the main, this is true. In many other instances, however, the attacks, especially in young children, are accompanied by high temperature, at times reaching 103° or 104° F., which, with the rapid breathing and the appearance of severe illness, leads to the diagnosis of pneumonia. Elevated temperature is, of course, only extremely rarely a part of uncomplicated adult asthma, and careful laboratory

*Read before the American Association for the Study of Allergy, Washington, D. C., May 16, 1927.

and physical examinations so far have revealed no other etiologic factors in these children with febrile asthma. In addition, the prolonged expiratory effort, typical of the adult asthmatic paroxysm, is frequently not seen in young children, especially infants, being replaced by what is apparently an ordinary dyspnea. Generalized râle formation would not bar out a pneumonia; and unless by one means or another definite areas of consolidation are made out, the differential diagnosis may be a matter of doubt. Relief to the difficulty of breathing by the use of epinephrin, of course, solves the problem. That this point is not one of mere academic interest is shown from the fact that in at least half of my cases of children with chronic asthma, a history is given of one or more past pneumonias, in one of my cases four such attacks, the last of which I had the privilege of witnessing. In spite of what seemed a fairly definite unilateral chest percussion dullness, the dyspnea yielded promptly to adrenalin, the temperature disappearing a day or so later. The frequency of the pneumonic histories, three or four attacks in a single young child with a negative chest examination and a negative x-ray picture, and the number of cases in which such a history is given, make it highly probable that many of the pneumonias were actually attacks of febrile asthma. Unfortunately all of my cases of this type so far have been seen where roentgen-ray facilities were not available at the time of the attack. The blood count in these cases may or may not reveal eosinophilia. Leucocytosis is usually present.

That this syndrome does not necessarily indicate a complicating pyogenic infection, is seen from the fact that in the use of sterile pollen extracts for desensitization purposes I have seen several high febrile attacks in children accompany the hay fever and asthma resulting from injudicious overdosage, in one instance, some five or six such attacks.

In a child with previous asthma or a definite asthmatic family history, this point of the presence or absence of actual pneumonia should not and probably would not be overlooked. With the initial asthma paroxysm in a young child, the differential diagnosis may be difficult. In view of the prompt relief available by the use of epinephrin, and the incorrectness of fresh air, outdoor treatment during a pollination season, the importance of this point is obvious. I have seen no harm resulting from a trial diagnostic dose of epinephrin in actual lobar pneumonia in asthmatic children.

Treatment Dosages.—For temporary relief in children, somewhat smaller hypodermic doses of epinephrin are required than in adults. I have on several occasions given six or seven minim dosages of this drug without ill effects to infants only a few months old. For permanent relief, however, just as high doses of pollen extracts for desensitization are needed and as well borne. I have in many instances, without unusual difficulty or the slightest harm, reached in children the full dosage of 1 to 2 c.c. of a standard strength 1:20 ragweed extract, the usual protective dose required in my community. Morphine or opium derivatives are rarely required in the asthma of children.

Preceding Bronchitis.—The initial pollen asthma in children is usually or almost invariably preceded by a history of cough or bronchitis of months' or years' duration. I have had occasion to see the condition in children whose

parents were under treatment for hay fever or asthma. There is nothing characteristic in the physical or Roentgen examination of the chest. The onset, recurrence or increase of symptoms during pollination seasons is the only clue in the history. The condition can be recognized by the accompanying vasomotor rhinitis and proved by the immediate alleviation of the condition by epinephrin dosages and its abeyance under an induced pollen-free environment, after usual bronchitis régimes and treatments have proved unavailing. The onset of asthma has been prophesied by me and verified in several such cases. As a confirmation, I have also produced a most annoying cough without asthma, lasting several days, by pollen extract overdosage in desensitizing children suffering from perennial hay fever, who had had neither previous accompanying bronchitis nor cough, in one case four such attacks. The cough in these cases bears a considerable resemblance to that of pertussis.

Vasomotor Rhinitis.—Pollen asthma in children is invariably accompanied or preceded by a definite vasomotor rhinitis. The history in these cases is one of almost constant or frequently recurring so-called "colds," with attendant intermittent or almost unceasing nasal blockage, frequently bilateral, but occasionally first on one side and then on the other, changing erratically, and never permanently unilateral per se. The discharge is watery or mucoid in character. In a case seen in a boy of twelve, after his second attack of asthma, the father of the boy, a physician, stated that the child had not been free from a cold for more than a year. Such a history is typical. In fact, several parents have recalled that the condition has existed since birth. Typical severe seasonal hay fever, with persistent sneezing and streaming eyes and noses, is not common in children as it is in adults. In children even ordinary seasonal hay fever is astonishingly mild. Nose rubbing and picking is common in these cases from the itching caused by the lysis of pollen granules on the susceptible nasal mucosa. The ocular, palatal and aural irritation of adult hay fever is seldom seen in children. Mouth breathing is exceedingly common. The condition, clinically, closely resembles typical adenoid disease, but is not relieved by adenotonsillectomy. In but few of the childhood asthma cases of this series has this mild vasomotor rhinitis been previously detected, though its presence was later invariably confirmed by competent nasal specialists. The diagnosis of this condition can be made out, and the pollen etiology established by the rapid betterment or clearing of the condition wtihin a few days under a pollen-free environment, and its recurrence through intentional atmospheric or laboratory pollen contact. The appearance of the nasal mucosa is characteristic if seen immediately after such pollen contact. Complicating purulent parasinusitis cannot be a common complication of these cases. I have seen only one or two instances.

Chronic Perennial Bronchial Asthma.—There is no essential difference in this condition in adults or children. The typical barrel-shaped emphysematous chest with bulging sternum often develops in early childhood.

Cutaneous Symptoms.—Urticaria and erythema are occasionally seen in adult asthma or a history of a few such attacks in securable. Eczema is exceedingly rare. On the other hand, in children angioneurotic edema is very

rare, and urticaria seldom occurs, but present eczema extending over many years, often dating back to infancy, or a history of eczema limited to infancy, is exceedingly common. These cutaneous lesions, both in adults and children, frequently clear under proper pollen treatment without attention to diet or local skin treatment.

Pollen Toxemia in Children.—In many children, the physical discomfort and disability are the sole effects of pollen hay fever and asthma, even in severe chronic cases. In addition, however, there appears to be a definite toxic syndrome from constant pollen antigen absorption, to which I have called attention in a recent article.[1] Besides the ordinary vasomotor rhinitis and typical chest findings of asthma or emphysema, these children show marked deficiency of weight, growth and development. The complexion is sallow or of a saffron tinge, the whole appearance greatly resembling that of hereditary syphilis or severe hookworm disease. I have not been able to find anything characteristic in these cases from a laboratory point of view. The most remarkable result of this toxemia is psychic. The mentality is decidedly substandard. Wild spells of anger alternate with long periods of listlessness. These children are extremely cross, irritable and intractable, on the whole in many ways resembling morons. The appetite is poor and capricious. Nocturnal enuresis seems a common accompaniment of the condition. I have seen it persist until after the onset of menstruation. This toxic state seems limited to children, and is seen in hay fever as well as in asthma.

Under a pollen-free environment within a few days, or at the most one or two weeks, with alleviation, but long before the complete elimination of the hay fever and asthma, the toxemia clears. Within even this brief period of time, these children become bright, cheerful and playful. The complexion becomes normal. Appetite returns and weight is rapidly gained. The radical improvement in so short a time has been expressed to me by several mothers as being almost miraculous. The enuresis corrects itself slowly, persisting during desensitization treatment usually as long as any allergic symptoms last, though I saw it clear permanently in one child of eight after only six weeks of such treatment. Shannon[2] and Piness and Miller[3] have called attention to a similar toxemia in allergic conditions in children, not necessarily of pollen origin.

Diagnostic Skin Tests.—These were performed intracutaneously in all the cases of this series, and this method of testing was found perfectly practical even in infants, using the back instead of the arm.

It was found as a rule that the typical positive reactions were of smaller size in children than in adults, and as in adults with definite pollen hay fever and asthma, were also at times, especially in young infants, completely negative both immediately and at the end of twenty-four hours. This condition of negative skin tests in pollen asthma was first called attention to by Miss Grothaus and myself in 1925[4] and 1926.[5] Peshkin[6] confirms this finding. The reason for this state of affairs, in the light of our present knowledge, is uncertain. Hypodermic tests with pollen extracts seem to me much more, in fact, perfectly reliable, both in adults and in children. The conjunctival test

with pollen extracts I have not found of much value in either adults or children.

In determining the actual symptom etiology of these hay fever or asthmatic children, it was found that the positive skin tests to feathers, animal epithelial emanations and orris root were practically always of clinical significance by actual contact demonstration. Removal of such contact, however, did not affect the clinical hay fever or asthma, making additional etiology, of course, obvious.

The frequent positive reactions to one or more foods were of clinical asthma significance, curiously enough, in not a single case of this series. That is, the use of such specific foods showing positive skin tests would not produce the asthmatic state nor did abstention from such foods abate the asthma. The ingestion of such specific positive skin test foods, however, was frequently known to produce indigestion or vomiting, or had done so in the past. This was true also of foods such as milk, egg and honey, even when the skin tests for such foods were negative. The past production or increase of eczema after certain foods in young children was a common story. Peshkin, in a study of 100 asthmatic children, about 30 per cent of whom were pollen cases, comes to the same conclusion.[7]

The pollen etiology of these cases was demonstrated by the history, intra- and hypodermic tests, the experimental induction of the condition by pollen contact, its abatement or relief under an experimental pollen-free environment, the details of which have been taken up elsewhere,[8] and by the results of pollen desensitization treatment.

Differences in Degrees of Pollen Sensitiveness in Adults and in Children.—Practically, of course, this is difficult to measure. The hypodermic use of pollen extracts up to the point of reaction and symptom production during a period of freedom is the best present method of gauging this point, and its measurement in untreated cases over a period of years is obviously not feasible.

While food sensitiveness is ordinarily gradually outgrown, the reverse is true of pollen cases living in a heavy, constant pollen environment. The histories of such cases living over a period of years in the same homes or communities, usually show a definite, constant, consistent yearly increase in the frequency and severity of asthmatic and hay fever symptoms. Rarely is natal pollen sensitiveness extreme. If such natal extreme sensitiveness were common, pollen cases should show severe and frequently recurring symptoms in the first year, which is not the case. Though I have seen bronchial asthma as early as the third week of life, and a number of other cases before the end of the first year, usually definite asthmatic symptoms do not occur until the child is at least three or four years of age.

If this initial natal sensitiveness be mild, and it apparently is, then following the initial pollen hay fever or asthma symptoms in children, relief should be practical by reducing pollen dosage by environmental precautions in the home without desensitization treatment or climatic changes. As a matter of fact, the possibilities of such relief are excellent in these early stage chil-

dren. I see a number of such cases in young children each year, who, under environmental pollen precautions alone, remain in such manner clear entirely, or with only rare, easily controlled attacks, not over one or two each year.

Initial pollen asthma attacks seldom occur in adult life, where there has not been accidentally a change to a heavier pollen environment. In my experience, however, symptom relief by purely household pollen dosage reduction is rarely of avail, certainly not occurring nearly as frequently as with children. On the whole, I feel it safe to say that pollen sensitiveness under constant atmospheric pollen dosage increases with age, especially where atmospheric antigenic pollen is perennial, or practically so. As a matter of fact, resistance to such pollen dosage in an identical environment in potentially hypersensitive cases with positive skin tests, is occasionally tolerated well into adult life before symptom production ensues, even in rare cases until past the age of 60, and in two instances in my records until past 70. One, an asthmatic of 72, with asthma of two years' duration, who, when first seen, had not had a clear day for weeks, secured complete relief in two or three days after removal to a pollen-free environment.

CONCLUSIONS

In childhood hay fever and asthma, the following differences are noted from the adult types:

1. High temperature occasionally accompanies the asthmatic paroxysm. This, with the attending dyspnea, often leads to the mistaken diagnosis of pneumonia. The required dosages of palliative hypodermic epinephrin treatment are somewhat smaller than in adults. Pollen extract desensitizing doses are identical in adults and in children.

2. A definite bronchitis of months' or years' duration antedates the initial asthma attack.

3. A definite toxemia, with typical physical and mental symptoms, occurs coincidently in many cases.

4. The accompanying vasomotor rhinitis is much milder than that of adult seasonal hay fever, consisting of more or less constant nasal blockage with mucoid discharge.

5. Complicating purulent sinusitis is rare.

6. The degree of pollen sensitiveness increases with age.

REFERENCES

[1]Kahn, I. S.: Pollen Toxemia in Children, Jour. Am. Med. Assn., Jan. 22, 1927, lxxxviii, 241.
[2]Shannon, W. R.: Neuropathic Manifestations in Infants and Children as a Result of Anaphylactic Reaction to Food Contained in Their Dietary, Am. Jour. Dis. Child., July, 1922, xxiv, 89.
[3]Piness, George and Miller, Hyman: Allergic Manifestations in Infancy and Childhood, Arch. Ped., Sept., 1925, xlii, 9.
[4]Kahn, I. S., and Grothaus, E. M.: Studies in Pollen Sensitiveness, Med. Jour. and Rec., June 3, 1925, cxxi, 664.
[5]Kahn, I. S., and Grothaus, E. M.: Fallibility of the Intradermal Tests With the Grasses in Chronic Perennial Bronchial Asthma, Med. Jour. and Rec., March 3, 1926, cxxiii, 290.

[6]Peshkin, M. Murray: Asthma in Children. I. Etiology, Am. Jour. Dis. of Child., June, 1926, xxxi, 763.

[7]Peshkin, M. Murray: Asthma in Children. II. The Incidence and Significance of Eczema, Urticaria and Angio-Neurotic Edema, Am. Jour. Dis. Child., Dec., 1926, xxxii, 862.

[8]Kahn, I. S., and Grothaus, E. M.: Fallibility of the Intradermal Tests With the Grasses in Chronic Perennial Bronchial Asthma, Med. Jour. and Rec., March 3, 1926, cxxiii, 290.

FURTHER OBSERVATIONS ON THE TREATMENT OF HAY FEVER WITH EPHEDRIN*

By Fred W. Gaarde, M.D., and Charles K. Maytum, M.D.†
Rochester, Minn.

THIRTY-SIX patients with autumnal hay fever were treated with ephedrin hydrochloride used internally in capsules, each containing 25 mg., or applied locally in the form of a nasal spray, using a 3 per cent solution. Eleven patients had had preseasonal treatment with only partial relief of symptoms; thirteen patients used both capsules and spray; twelve patients used spray only; and eleven patients used capsules only. Therefore, twenty-four patients used the drug by mouth and twenty-five by local application.

The untoward results varied greatly with different patients. Nervousness and tremor were noticed in thirteen cases, tachycardia or palpitation in five, weakness, faintness, or giddiness in four, sleeplessness in two, increased perspiration in three, stimulation in two, and nausea in one.

In 70 per cent of the cases the untoward symptoms were absent or mild, while in four cases the nervous symptoms were marked. In this group the nervous symptoms produced by small doses are out of proportion to those obtained with much larger doses in conditions other than hay fever. The following interpretation was suggested: (1) the nervous symptoms bore a distinct relationship to the neurotic tendency of the patient; (2) patients with hay fever are already in a highly nervous state, and (3) the patients treated were all active while other observations have been made on bed patients.

RESULTS OF EPHEDRIN BY MOUTH

Twenty-four patients (54 per cent) with hay fever were completely or almost completely relieved for four hours or more; seven (29 per cent) were partially relieved, and four (16 per cent) were not relieved or they were unable to tolerate the nervous symptoms.

Ten patients had asthma with hay fever; five were relieved by ephedrin; three were moderately relieved, and two were not affected.

---

*Abstract of paper read before the American Association for the Study of Allergy, Washington, D. C., May 16, 1927.

†Division of Medicine, Mayo Clinic, Rochester, Minn.

Received for publication, August 10, 1927.

RESULTS OF EPHEDRIN BY SPRAY: 3 PER CENT SOLUTION USED SEVERAL TIMES A DAY

Sneezing was marked in 12 per cent of the patients. Seven patients (28 per cent) were markedly relieved for several hours; twelve (48 per cent) were partially relieved for several hours or completely relieved for less than an hour, and six patients (24 per cent) were not benefited.

Ephedrin given by mouth in 25 mg. to 60 mg. dosage afforded temporary relief to slightly more than 50 per cent of the patients with autumnal hay fever. An additional 25 per cent were sufficiently relieved to consider its use warranted. Ephedrin given in a 3 per cent solution as a nasal spray is less efficacious and the relief is shorter. Most of the patients, however, felt that it added to their comfort. The best results were obtained when the spray was used early in the paroxysm. The effect of both the local and internal administration seemed to depend upon the severity of the paroxysms, and the good results were obtained in the milder seizures. Eleven patients who obtained only partial relief from preseasonal treatment were able to control their symptoms with the occasional use of ephedrin. The neurotic temperament and nervous state of the patient are important factors in the production of tremor, rapid heart action, and other distressing symptoms produced by the drug.

Although the value of ephedrin is limited and its effect temporary, the observation of fifty-five patients during two seasons warrants the conclusion that the drug should be given a definite place in the symptomatic treatment of autumnal hay fever. It should be emphasized that when good effects are obtained they are temporary and symptomatic.

LABORATORY METHODS

AN APPARATUS FOR RAPID QUANTITATIVE ROUTINE DETERMINATION OF ALBUMIN AND SUGAR IN URINE*

By James J. Short, M.D., New York City

THERE are several methods in common use for determining the presence of albumin in urine. With each of these it has been the time-honored custom to note roughly the quantity present by the use of such terms as "faint trace," "trace," "moderate amount," "large amount," etc. Naturally the report rendered depends largely upon the individual making the test. What one might report as a "trace," another would call a "faint trace" and so on. For the sugar determination, Benedict's qualitative copper solution is widely employed. Slight reductions are very frequently reported as a trace. Quantities above 0.2 per cent are usually determined by some quantitative procedure.

A rather widespread movement has been started by the insurance companies to eliminate the variations resulting from personal factors by instituting routine quantitative methods, both for sugar and albumin. Kingsbury, Clark, Williams and Post[1] recently reported a method for the routine quantitative determination of albumin in urine. This is based upon a method devised by Folin and Denis[2] and consists of the addition of 7.5 c.c. of 3 per cent sulphosalicylic acid to 2.5 c.c. of urine, using tubes of uniform diameter. After mixing, the tubes are allowed to stand ten minutes, and the turbidity produced in each is compared in a Clark lamp[1] with standard tubes. The standards range from 5 mg. to 100 mg. of albumin per 100 c.c., and the unknown is reported in these terms.

For routine quantitative sugar determination many laboratories have adopted the Benedict picric acid-acetone method.[3] This is a colorimetric method and gives a color with normal urine—the so-called normal sugar of urine. One c.c. of urine is employed, and the final dilution is up to 25 c.c. in a specially made test tube graduated at the 25 c.c. mark. A comparison is then made with standards in tubes of the same diameter.

The method devised by Sumner[4] seems preferable to the above for routine work. It is simple, apparently very accurate and seems to give lower and somewhat more consistent results than that of Benedict. The technic is similar and is as follows:

One c.c. of urine is pipetted into the same 25 c.c. graduated tube described above. Three c.c. of the Sumner dinitrosalicylic acid reagent are then

*From the Laboratories of the Life Extension Institute, New York.
Received for publication, August 10, 1927.

added, the contents mixed and the tube placed in a boiling water-bath for five minutes. It is then cooled, diluted to 25 c.c., mixed and compared with the standard tubes of equal diameter in a comparator. Sumner says with reference to the interpretation of results by this method: "Concentrated urines, containing over 0.18 per cent of sugar, or dilute urines, containing over 0.12 per cent of sugar, can be considered abnormal."

It goes without saying that any accurate quantitative method greatly increases the time required for its completion over a qualitative method. Single pipettings require an immense amount of time and make routine quantitative procedures on urine prohibitive, unless the laboratory has unlimited resources of space, personnel and equipment. Apparatus* has therefore been devised

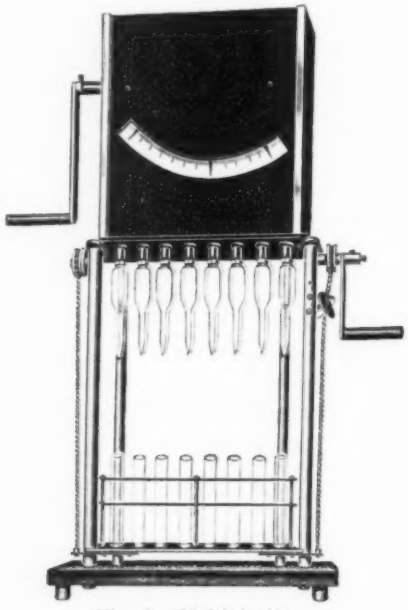


Fig. 1.—Multipipette.

to make 16 pipettings at one time, with speed, precision and without sacrifice of accuracy. Fig. 1 is an illustration of one such apparatus. Two such pieces of apparatus are necessary for the albumin and sugar methods described in this paper—one apparatus to pipette the urine into the albumin and sugar tubes and both to pipette reagents. A specially designed test tube rack constructed of bakolite has been devised for use with this apparatus (Fig. 2). Bakolite seems ideal for this purpose as it is tough, does not corrode, withstands great mechanical injury without fracturing and does not soften with boiling.

Briefly, the routine for sugar and albumin with the multipipette is as follows: urines are poured into 15 c.c. conical centrifuge tubes, placed in two high-powered centrifuges having a total capacity of 16 tubes and centrifuged.

*The apparatus described in this paper together with special bakolite racks and modified Clark lamps are manufactured by the Klett Manufacturing Company, 202 East 46th Street, New York, N. Y.

They are then placed in the bakolite 16-holed rack and taken to the first pipetting apparatus. This apparatus has 16 vertically placed record syringes of uniform size connected to glass pipettes as illustrated. The lever at the left of the apparatus actuates all 16 plungers simultaneously. A dial records the amount of fluid drawn into the glass pipettes. Three and five-tenths c.c. of urine are drawn into each of the 16 pipettes of the first apparatus from each of the 16 centrifuge tubes. The rack containing centrifuge tubes is then withdrawn from the apparatus and the albumin rack containing 16 of the specially graduated albumin tubes* is placed in the apparatus. Two and five-tenths c.c. of urine are then discharged into each of the albumin tubes, the indicator on the apparatus moving from 3.5 to 1 c.c. The albumin rack is then withdrawn and the rack containing the 25 c.c. sugar tubes* is placed in the apparatus, each tube receiving the remaining 1 c.c. of urine. After this the apparatus is rinsed with distilled water contained in a 2-liter tray which is a part of the apparatus. The rack containing albumin tubes is next taken to the larger apparatus. This is identical with the first apparatus except for greater capacity. Seven and five-tenths c.c. of 3 per cent sulphosalicylic acid are drawn into each of the pipettes from a tray holding about 2 liters. (This tray is refilled from time to time from a large reagent bottle

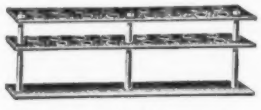


Fig. 2.—Bakolite rack.

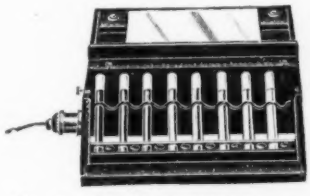


Fig. 3.—Modified Clark lamp.

and syphon.) The albumin rack is placed under the pipettes and each tube receives exactly 7.5 c.c. of the reagent. The rack is allowed to stand for ten minutes and the turbidity then compared with standard tubes having turbidity values equivalent to 5, 10, 20, 30, 40, 50, 75, and 100 mg., of albumin per 100 c.c.* A modified Clark lamp as illustrated is used in this comparison.

The rack of sugar tubes each containing 1 c.c. of urine, as noted above, receives 3 c.c. of the Sumner reagent from the first apparatus. It is then placed in a boiling water-bath for five minutes which causes a dark reddish-brown color to develop, the intensity depending upon the amount of sugar present. After cooling the rack is taken to the larger apparatus. Twenty-one c.c. of distilled water are drawn into each of the pipettes and discharged into the sugar tubes making the total volume in each 25 c.c. They are then compared with standard tubes equivalent to 0.05, 0.1, 0.2, 0.3, 0.4 and 0.5 per cent of sugar.† Should the amount run higher than 0.5 per cent in the

*The albumin and sugar tubes used in this procedure must be of standard caliber and accurately graduated. Tubes manufactured by Fales Chemical Company, Shore Road, Cornwall Landing, N. Y., have been found very satisfactory. Permanent standards for the albumin determination are also prepared by this company according to the method described by Kingsbury[1].

†These standard tubes can be developed from glucose solutions of the indicated percentages. One c.c. of each is treated in the same manner as the 1 c.c. of urine. A set of such standards will not change appreciably for several hours. Preliminary experiments in the development of permanent standards indicate that Bismark Brown is satisfactory for this purpose—prepared by diluting a concentrated solution to match each of the sugar standards. Dr. Sumner has recently developed permanent standards, using copper sulphate, iron, alum, and dinitrosalicylic acid, which are very satisfactory.

preliminary test, the urine is diluted to fall approximately within the range of standards and the test repeated singly.

COMMENT

Actual use of these methods in the analysis of several thousand specimens has given us great confidence in the apparatus and in the procedures. The saving of time is enormous. The accuracy is fully as great as could be obtained by single pipettings. Comparison with previous routine qualitative procedures for sugar and albumin shows that the above outlined procedures can be carried out even more quickly. In the analysis of identical specimens by different workers the albumin and sugar reported have agreed very closely; this takes away the former variations due to the personal element and results in a higher standardization of procedure.

REFERENCES

[1]Kingsbury, F. B., Clark, C. P., Williams, G., and Post, A. L.: The Rapid Determination of Albumin in Urine, Jour. Lab. and Clin. Med., 1926, xi, 981.

[2]Folin, O., and Denis, W.: The Quantitative Determination of Albumin in Urine, Jour. Biol. Chem., 1914, xxiii, 273.

[3]Benedict, S. R., and Osterberg, E.: A Method for the Determination of Sugar in Normal Urine, Jour. Biol. Chem., 1921, xlviii, 51.

[4]Sumner, J. B.: A New Specific Reagent for the Determination of Sugar in Urine, Jour. Biol. Chem., 1925, lxv, 393.

DEPARTMENT OF REVIEWS AND ABSTRACTS

ROBERT A. KILDUFFE, M.D., ABSTRACT EDITOR

CLINICAL AND EXPERIMENTAL

ALBUMINURIA: Albuminuria in Children, Calvin, J. K., Isaacs, B. L., and Meyer, J. Jour. Am. Med. Assn., June 12, 1926, lxxxvi, 1821.

The significance of albumin in the urine of apparently healthy children is the subject of much discussion.

The authors, after an extended study, offer the following classification:

Benign albuminuria:

1. Malnutrition albuminuria, frequently associated with anemia, underweight, and systolic basal murmur.

Foci of infection, especially infected tonsils, adenoids, nasal sinuses, and carious teeth are common causes of this malnourished condition.

2. Orthostatic albuminuria associated with posture.

3. Idiopathic or "growth albuminuria," including the terms juvenile, puberty, cyclic, transitory, and intermittent.

Borderline fluids contain 75 to 100 mg. per 100 c.c. (0.015 to 0.02 c.c. in 2 c.c.). This slight increase in the protein content may or may not be significant. Cerebral arteriosclerosis, postepileptic seizure states, encephalitis, head injuries with cerebral edema, treated inactive neurosyphilis, psychoneurotic-like states with toxic foci, alcoholism, multiple sclerosis, degenerative spinal-cord conditions and other neurologic conditions at times give this borderline reading. This moderate increase in total protein is of value in differentiating between organic and functional conditions. A positive increase favors an organic diagnosis.

Neurosyphilis (a) Paresis. In this group is found the highest protein content with the exception of the meningitides, xanthochromic fluids and neuronitis cases. The average paretic fluid gives a reading of 200 mg. per 100 c.c.

(b) Tabes Dorsalis. The protein estimations in this group have not given high readings. The lowest in treated cases give normal readings the highest 175 mg. per 100 c.c. It is well known that inactive tabes may give completely negative serologic findings. It is rare not to find the protein content increased in tabes and we have found it an aid in a questionable case where the Wassermann was negative.

(c) Cerebrospinal Types. This group consists of the meningovascular cases. The meningitic forms give the highest readings in this group. As a rule the total protein content is not as high as in the paretic group, ranging from 75 mg. to 275 mg. per 100 c.c. An average is about 125 mg. per 100 c.c.

Cerebral Arteriosclerosis. This group includes nonsyphilitic thromboses, organic dementia, aphasies and so forth, usually old lesions. As a rule the protein content is moderately increased.

Epidemic Encephalitis. In all the positive acute cases a moderate to a marked total protein increase was noted. In the chronic cases the protein content was frequently normal. The pathologic readings averaged 125 mg. per 100 c.c. No parallelism was seen between high-cell counts and excess protein. Sugar content readings have not been consistent.

Acute Polyneuritis. In the low-grade toxic or infectious multiple or mononeuritis cases the protein content has usually been found only moderately increased, about 100 mg. per 100 c.c.

(a) Neuronitis or Central Neuritis. In the acute neuronitis cases the readings averaged 450 mg. per 100 c.c.

Brain and Spinal-Cord Tumor. The brain-tumor cases almost invariably showed a moderate increase in protein, about twice normal, 100 to 150 mg. per 100 c.c. One case of syringomyelia with xanthochromic fluid gave an extremely high content, 700 mg. per 100 c.c., and one case of glioma with rupture by hemorrhage gave a high-protein reading. The cord tumors where obstructive give high readings as do other xanthochromic fluids. One cord tumor with evidence of hydrodynamic block gave a lumbar reading of 800 mg. per 100 c.c. and a cisterna magna reading of 100 mg. per 100 c.c.

Epilepsy. These are all cases in which organic factors were suspected but none found except some complicating toxic factors; such as infection, alcohol and so forth. This group showed protein determinations slightly above normal. Following a convulsion the protein content has been more definitely increased.

Cerebral Edema. The alcoholics with mental symptoms have all shown increased protein content. The same applies to head injuries showing increased manometric pressure readings. This is a transudative protein excess. The protein readings are about twice normal in these cases.

Meningitis. The purulent meningitides give the highest readings. Serous meningitis has consistently shown two to three times normal protein content.

Degenerative Spinal-Cord Diseases. (a) Multiple Sclerosis. Only a moderate increase in the protein content was found in these cases. Often the reading is normal. No relationship between colloidal-gold curves and increased protein content was seen.

(b) Combined Sclerosis. Slight increase in the protein content may be found, but the reading is more often normal.

A reduction in the protein content is an early evidence of serologic improvement.

The method described, though giving slightly higher readings, checks very closely with the Denis-Ayer method and is, the authors believe, the more practical clinical procedure.

BILE, BACTERIOLOGY OF: Studies in the Bacteriology of Bile, Hansen, S. Hospitalstend, Copenhagen, April, 1926, lxix, 289.

A total of 41.4 per cent of samples of bile obtained from autopsies and examined by the author revealed traces of infection.

In some instances this infection is said to have occurred in and to have exhibited an apparent connection with presence of bile, of which it was assumed as the result, while in others the ability of colon bacilli found in bile to live for from six to nine months in the latter was regarded as a probable indication of their viability in such a medium.

Examination of bacterial content of samples of bile collected during operations for gall stones is declared to have demonstrated that 42.5 per cent of these were infected.

Stones of recent development was a a rule encountered together with sterile bile in the gall bladder, a fact which in the opinion of Hansen appears to oppose the view of the importance of infection in formation of gallstones. Old stones were found almost invariable in gall bladders which presented evidences of inflammatory alterations and contained infected bile, an observation which according to Hansen seemed to point to the existence of a secondary infection.

REVIEWS

Books for Review should be sent to Dr. Warren T. Vaughan, Medical Arts Building, Richmond, Va.

*The Beloved Physician**

THE biography of Sir James Mackenzie, written by one who knew his subject from an intimate personal acquaintanceship and who possesses the happy faculty of telling his story in a dramatic manner, and Mackenzie's life was indeed dramatic.

A biographic sketch based on the volume under review will be found in the editorial pages.

To all physicians who love medical biography, and every physician should so classify himself, this work will be delightful reading. The author's frequent use of superlatives and his obvious exaltation of his subject do not detract from the pleasure of the book.

Principles of Diagnosis and Treatment in Heart Affections†

THE fourth edition of this work has, since Mackenzie's death, been brought to date by his successor at St. Andrews, James Orr. The work differs from Mackenzie's more elaborate contribution, *Diseases of the Heart*, in that it is written primarily for the practitioner of medicine and provides information which is throughout of an eminently practical nature. As in his other works Mackenzie goes at once to the heart of the matter. Without preliminary *tuning up* on anatomy, embryology, histology, physiology and the like, he jumps directly into a discussion of heart failure. Indeed it is heart failure which is uppermost in the minds of all victims of heart disease and therefore in the minds of their professional advisors. When will it occur; how may it be prevented; is this particular case one that is likely to experience heart failure; what must be done?

Following this are sections devoted to disordered cardiac activity, myocardial affections, prognosis and treatment.

Reports of the St. Andrews' Institute for Clinical Research, Vols. 2 and 3‡

THE St. Andrews' Institute more recently renamed the James Mackenzie Institute for Clinical Research was established in the little town of St. Andrews, Fife, for the purpose of studying disease in its incipiency. The little town was selected in great part because of the permanency of its population. Mackenzie has always been particularly interested in prognosis and insisted that the earlier pathologic changes are recognized the more accurate will be our prognostic deductions. "Prognosis is the motive which inspires note taking with the breath of life, making the notes a perennial source of knowledge that can be applied in the practice of medicine."

*The Beloved Physician, Sir James Mackenzie. A Biography by R. McNair Wilson. With a photogravure. Cloth. Price, Pp. 316, $4.00. TheMacmillan Company, New York, 1926.

†Principles of Diagnosis and Treatment in Heart Affections. By Sir James Mackenzie, M.D., F.R.C.P., Ab. and Ed., F.R.C.P.I. (Hon.) Director St. Andrews' Institute for Clinical Research, Consulting Physician to the London Hospital, Consulting Physician to H. M. The King of Scotland and Orr, James, M.B., Ch.B., Physician to The St. Andrews' Institute for Clinical Research. Third Edition. Cloth. Pp. 242. Price $3.50. Humphrey Milford, Oxford University Press. American Branch, New York.

‡Reports of the St. Andrews' Institute for Clinical Research. (Volume II. Cloth. Illustrated. Pp. 190. Price $3.00.) (Volume III. Cloth, Illustrated. Pp. 227. Price $3.00.) Oxford University Press, American Branch, New York.

Volume two of the reports deals chiefly with the principle of the reflex arc and presents a large amount of clinical and experimental evidence bearing upon this hypothesis. This line of thought also runs through volume three, but in both books there are articles on other non-related subjects. In all of them, however, we see clearly the endeavor to study the earliest changes, and if the work of the institute is successful in following the aims of its founder, the magnum opus of the report may not be expected to appear for another twenty or thirty years or more, until after the accumulation, sifting and studying of a tremendous mass of contemporary case records.

This should not and does not interfere with the publication of other investigations, and as we have stated these are devoted especially to the early manifestations. Thus we find articles on the normal infant's chest, clinical studies of influenza, the role of the lymph gland in the absorption of foreign particles and tubercle bacilli (the first defense barrier), the effects of environment on the nervous system of infants and children, clinical manifestations of defective blood supply to voluntary muscles, papers dealing with records obtained in a boarding school for girls, and the like.

*Some Recent Works on Ultraviolet Light**

ULTRAVIOLET light treatment is not new. Its experimental use has extended over more than two decades. We have now reached the stage of its popularization, of its rational and sometimes irrational application to a wide variety of clinical conditions, and of the appearance in the literature of historical and encyclopedic compilations summarizing the observations made to the present time. Among these four in particular may be mentioned as covering the field in sufficiently exhaustive detail.

The work of Francis Howard Humphris[1] does not go into extensive detail but is of interest as presenting a British point of view and as being thoroughly practical from a clinical viewpoint.

The volume by Luckiesh and Pacini[2] conveys the impression of being written in part at least for the layman and is in spots obviously colored with hyperenthusiasm and claims which, if they are not exaggerated, are certainly not as yet supported by the experimental evidence. There are a few errors of fact, none of great importance, such as might be expected with layman writing on medical subjects. The book, however, is very pleasant reading, is authoritative except where it relates to theories of disease, and may be well recommended.

The third work by Edgar Mayer[3] is by far the most exhaustive and authoritive of the three. At the same time it is the most difficult of the three to follow, chiefly because of the extremely large number of excerpts from literature, which we feel at times might have been more systematically grouped. We trust that in his next edition the author will enlarge upon his "chapter summaries," a step which will greatly reduce this disadvantage. The author presents a great deal of original experimental work particularly in the treatment of all forms of tuberculosis. The book is well illustrated. The bibliography is complete.

The three books together with the work by Rollier,[4] previously reviewed in these columns, will make a quite complete reference library for the student of actinotherapy.*

*For further remarks see editorial pages of this issue.

[1]Humphris, F. H., Artificial Sunlight. Cloth. Pp. 184, with 12 illustrations. Price $2.75. Oxford University Press, American Branch, New York.

[2]Light and Health. A discussion of Light and Other Radiations in Relation to Life and Health. By Luckiesh, M., and Pacini, A. J. Illustrated. Cloth. Pp. 302. Williams and Wilkins, 1926.

[3]Mayer, Edgar. Clinical Applications of Sunlight and Artificial Radiation. Cloth, $10. Pp. 550, with illustrations. Williams and Wilkins, 1926.

[4]Heliotherapy with Special Consideration of Surgical Tuberculosis by Rollier, A., M.D. Cloth, Pp. 318. Price $6.25. Oxford University Press, American Branch, New York.

The Journal of Laboratory and Clinical Medicine

VOL. XII ST. LOUIS, MO., SEPTEMBER, 1927 NO. 12

Editor-in-Chief: WARREN T. VAUGHAN, M.D.
Richmond, Va.

ASSOCIATE EDITORS

DENNIS E. JACKSON, M.D. - - - - CINCINNATI
PAUL G. WOOLLEY, M.D. - - - - - - LOS ANGELES
J. J. R. MACLEOD, M.B. - - - - - - - - TORONTO
W. C. MACCARTY, M.D. - - - - ROCHESTER, MINN.
GERALD B. WEBB, M.D. - - - - COLORADO SPRINGS
VICTOR C. MYERS, PH.D. CLEVELAND
RUSSELL L. HADEN, M.D. - - - ROSEDALE, KAS.
JOHN A. KOLMER, M.D. - - - - - PHILADELPHIA
ROBERT A. KILDUFFE, M.D. - ATLANTIC CITY, N. J.
A. PARKER HITCHENS, M.D. - - - - MANILA, P. I.
DEAN LEWIS, M.D. - - - - - - - - BALTIMORE
GEORGE R. HERRMANN, M.D. - - - NEW ORLEANS
HAROLD D. CAYLOR, M.D. - - - ROCHESTER, MINN.

Official Organ of the American Society of Clinical Pathologists

Contents of this Journal Copyright, 1927, by The C. V. Mosby Company—All Rights Reserved
Entered at the Post Office at St. Louis, Mo., as Second-Class Matter

EDITORIALS

The Broader Aspects of Allergy

THE world marvels at those recent advances in physics, chemistry and engineering which have combined to make the present day so remarkable an era in which to live, but it is inclined to overlook the fact that in the ancient profession of medicine, dormant through the middle ages, the last century has produced equally remarkable achievements, advances in knowledge many of which have already been applied to the greater comfort and happiness of mankind. Not the least remarkable has been our acquisition of knowledge of those principles underlying the phenomena of immunity and their application in the relief of suffering.

Physiology, since its inception in the master work of Harvey, has been concerned with the vital activities of the living body. Its offshoot, biochemistry, began with the work of Lavoisier and von Leibig at the opening of the nineteenth century. The earlier work fell in the realm of physiologic chemistry with the study of those inanimate organic compounds which are built into vital substance and of the end-products which are discarded in the process of living,

together with a study of dead structures which once were living. This was in essence the application of organic chemistry to living structure, and the resulting information was indispensable, but from the nature of the experimental methods little knowledge was acquired of the actual processes of life itself.

For successful study of life, life must not be destroyed at the inception of the investigation. From physiologic chemistry the science of experimental biology has emerged. Here the endeavor is to study the living while still alive. In a crude way the contrast between these two divisions of biochemistry may be likened to the individual snapshots before, during and after a stated activity as contrasted with a cinema reproduction of all the stages and developments in the action.

We may look upon the science of immunology as a rather highly specialized division of the broader field of experimental biology. Immunology has far outgrown its descriptive designation and now includes the study of many phenomena in which immunity as the term is generally understood plays no part. One of these outgrowths from Immunology is that condition of many aspects known as allergy.

Facts are unchanging but our descriptions and interpretations of them are necessarily made in the light of our own past experience and must be altered to accord with more enlightened comprehension. The term immunology is fairly conclusive; and if used in the broader sense of freedom from disease of various sorts whether infectious or not, it may still be applied to the phenomena of clinical allergy. Anaphylaxis, coined by Richet as a term meaning "without protection," is no longer tenable as a descriptive title in view of our present understanding of the phenomena involved. Richet believed that the first injection of a foreign protein destroyed any natural resistance that the animal might possess against the hypothetic poison. The term, however, will remain in the literature, particularly since it is now used to designate a very definite chiefly experimental process characterized by antigen antibody reaction. Allergy, indicating as it does merely an altered reactivity, is more desirable as a generic term. It commits the user to no single explanatory hypothesis, and hypotheses there are aplenty. It would seem better to continue the use of these terms while realizing their descriptive deficiencies, devoting less energy to lexicographic disputations, particularly since we must realize that the designation of today will not be acceptable tomorrow. These terms and those which are employed along with them should at least suffice until our understanding of the subject has progressed to that stage where we can more confidently give specifically descriptive titles to every phase of the phenomena under study.

Indeed, the student in this field of experimental medicine is not primarily an immunologist, an allergist or an atopist, he is an experimental biologist in the truest sense of the term. He is studying life processes, vital actions and reactions in the living. Few others possess as excellent an opportunity for the study of life itself. The student of allergy is the student of life. True, his chief interest is in what would appear to be an alteration from the

normal vital activity. This we will acknowledge as long as we are discussing allergy as it is observed in man or animal, but the evidence would indicate that in their reaction to foreign allergens the *individual cells* of the body are behaving in a strictly normal manner. The abnormality is not within the cells but in their chemical and nutritional environment. Furthermore, as is so often the case in other fields of study, more can be learned of the normal from a study of deviations from normal than is gained from a study of normalcy itself.

One of the most important contributions on the origin of life and the development of species has recently been made by an immunologist, the groundwork of whose theory is his knowledge of the phenomena of infection and immunity.[1]

The chemistry of allergy is the chemistry of life and no allergist is truly constructive who does not see his way to supplementing his study with experimental investigations of the nature of vital activity. The clinical allergist may reply that he is dealing with human beings on whom he cannot experiment, but in truth he is doubly fortunate for his is the opportunity of both studying a naturally occurring manifestation and also correlating this with experimental animal investigations in his laboratory.

We regard as a statement which time will not disprove, that protein is the basis of life. Life does not exist without protein. The student of allergy must be a student of the chemistry of protein and of protein metabolism. The basis of vital activity as we study it today is enzyme action. The allergist must learn of enzymes. There are five fundamental phenomena common to all living substances. First, living protoplasm is oxidizable. Deprive it of its state of partial oxidation and it loses its fundamental properties of life. It will no longer conduct an impulse nor will it grow. It will not synthesize or will it move spontaneously. Its respiration ceases and its heat production stops. Second, living substance possesses the ability of synthesizing protein, carbohydrate, fat and other substances. It has the power of growth. This is the chemical process underlying reproduction. This synthesis usually occurs by dehydration. Two molecules are united or condensed by the elimination of a molecule of water, one of them giving off hydrogen and the other hydroxyl. Third, all living tissues possess the property of generating electric current. Every living cell is a battery. Fourth, all living substances possess the ability of producing enzymes, substances which accelerate chemical processes. Possibly it is by virtue of these enzymes that living substance accomplishes the reverse of synthesis, namely, hydrolysis. But hydrolysis occurs equally within the living substance. Last, the living substance possesses the power of assimilation, that is of building new homologous living structures from the constituents of dead heterologous substance.

The student of allergy must learn of all these things. Not until after we have learned much of life will we know much of allergy. The basis of the phenomenon is in the unit cell within the body. In allergic reactions this cell is reacting is an entirely normal way as far as the cell itself is concerned. The cause of the abnormal manifestation is an alteration in the life process of the cell, not "altered reactivity" as far as the unit of life is concerned, but

is an alteration in the chemical environment of the cell due to changes in the blood and the lymph. The cell is reacting normally to an altered environment.

A few years back when endocrinology was new and a fad, few diseases to which flesh is heir were omitted by the enthusiast as not being due in part at least to some endocrine disturbance. While the diseases in which allergy appears to be a factor are distinctly limited in number, their character shows such wide divergence that skeptics are inclined to smile. On the contrary it seems almost remarkable that allergy does not manifest itself in an even wider diversification of forms if we realize that we are dealing with a reaction in which many if not all the cells of the body, in widely different locations, are partaking in greater or less degree.

We now discuss anaphylaxis in terms of antigen-antibody reaction and allergy in terms of protein sensitization. The true conception will not be arrived at until we can discuss it in terms of intracellular activity, in terms of the chemistry or the physical chemistry, the energetics of the single cell.

We do not wish to imply that there are not other factors which must be taken into consideration. While the basic allergic reaction lies in the vital activity of the individual cell, the clinical explosion is tempered by modifying activities of different groups of tissues such as nonstriated muscle. This is further exemplified in the work of Manwaring, and of Weil and of Falls[2] showing the importance of the liver in the production of anaphylactic shock.

It appears not improbable, as more is learned of the normal activity of living protein and particularly of its enzyme reactions, that a reliable means may eventually be developed for the relief of clinical allergy by a single type of therapeutic procedure. Nonspecific desensitization has been widely discussed and often attempted, sometimes with startling success. Results have been inconstant and on the whole inconclusive. Peptone, bacterial vaccines, calcium chloride have each been recommended as nonspecific desensitizers in clinical allergy and have in the occasional case given undoubted relief. Peptone, trypsin, various inorganic salts, foreign proteins, urine, sodium chloride and sodium oleate have produced analogous results in experimental anaphylaxis. The explanations suggested have necessarily been in terms of existing concepts and but to mention them, include such as antianaphylaxis, antisensitization, lowering of the surface tension of the blood, interference with complement action, action on nerve cells, effect upon the colloidal state of the cells and fluids, reducing their irritability, reduction in the speed of reaction between antigen and antibody, alteration of the sensitivity of the reactive mechanism, and tissue inactivation when through exhaustion, drug action or other injury, the sensitized cell cannot respond to the antigen-antibody reaction. Possibly some time, when we have learned more of the chemical processes of life, a simple way may be discovered to modify them so that the reaction of the body cell to an abnormal chemical environment will not be harmful to the body organism as a whole.

The field for possible study and development in allergy, as in other studies of vital activity, appears quite limitless. Methods are already available and new ones are constantly being added. Acquired knowledge in the collateral sciences such as physical chemistry, plant biology, protein and colloidal chem-

istry, protobiology, are all available for application in the further study of allergy. We have but scratched the surface. The mysteries of life remain to be disclosed.

REFERENCES

[1]Vaughan, Victor C.: A Chemical Concept of the Origin and Development of Life, JOUR. LAB. AND CLIN. MED., to appear in the October, 1927, issue.
[2]Wells, H. Gideon: The Chemical Aspects of Immunity, The Chemical Catalog Co., New York, 1925.

—*W. T. V.*

Footprints

PERHAPS it has occurred to you that in his immortal *Psalm of Life* Longfellow has interpolated unnecessary cynicism, in intimating that even with the greatest, their impress is made but on the shifting sands and that all too soon the footprints will be lost forever. But Dr. J. C. Merriam, President of the Carnegie Institution, who has made one of the most comprehensive paleontologic studies of footprints, assures us that while the poet was quite in earnest, his meaning was altogether otherwise.

Long before the dawn of human existence, when the dinosaur was the lord of creation, these animals were wont to frequent the watering places. The heavy impress of their feet was molded into the moist sand. In some sheltered localities, with no human being and few animals of consequence to mar the markings, these footprints remained undisturbed for hundreds, nay thousands of years, until the sand had slowly hardened into stone. Longfellow had seen these dinosaur sandstone footprints in Connecticut and it was their permanence rather than their evanescence which so impressed him.

To the physician few studies are more interesting or more inspiring than that of the footprints left by the great men of medicine. No two stories are exactly alike although many are instructive in their parallelism. Others are absorbing, sometimes tragic, in their contrasts.

Not a little pathos surrounds the contrast between Marion Sims and George Harley, two notable contemporaries. Sims, son of a poverty-stricken Carolina farmer, made out as well as he might with a second rate education, nailed up his shingle in his home town and after the death of his first two patients, found it advisable to change his residence. Imagine his despair. In Montgomery, Alabama, he was no great success. But he had an idea. He thought that he saw a way to the cure of vesicovaginal fistula, that filthy, hopeless penalty of motherhood. Operation after operation was followed by failure after failure and Sims found himself the laughingstock of his Montgomery confrères. But he persisted.

Unable to obtain assistance he built himself a shack in the back yard which he called his hospital and in which he kept his half dozen faithful negro women, all afflicted with the same malady, each of whom would in turn assist when he tried out his most recent theory on her sister in affliction. This was all the operative aid he could muster.

At last he succeeded.

And then he found himself afflicted with an uncontrollable chronic diarrhea which nearly terminated his existence. From his own description we cannot say whether this was pellagra or sprue or an amebiasis or other chronic colitis. Probably it was not the diarrhea of pernicious anemia for he lived too long afterwards. But once again he was forced to change his abode, this time for the sake of his own health. He went to New York a poor man with no friends and no supporters. He watched his operation and his special instruments stolen from him by the surgeons of fashion in the great city.

He had the courage of his convictions, however, eventually elicited support, built a women's hospital and before his death found himself the great surgeon of the day, fêted and decorated by the ruling heads of Europe, his amphitheater the surgical mecca of the world.

George Harley, the wealthy son of an old family from the north of England, accustomed to all manner of luxury, nevertheless a man of brilliant intellect, procured for himself the best and most comprehensive medical education available. Not content he spent several years at the feet of the masters in the most prominent clinics on the continent.

When at last he had satisfied himself with the thoroughness of his preparation he returned to London, opened a consulting office in Harley Street, the most fashionable section of medical London, established the first chair of physiology in the world, in the University of London, and gave promise of becoming one of the greatest physiologists.

And in his thirties he went blind.

Sims and Harley; the contrast is pathetic.

Edward Livingston Trudeau who had nursed his brother night and day in his hopeless fight against consumption, carefully protecting him in accordance with the doctor's orders, from both the fresh air and sunlight, himself developed the dread disease. He betook himself to the mountains. He did not go there to fight tuberculosis, for in those days there was no fighting. He was a doomed man. His friends begged him not to go, for life in the mountains would but hasten his demise. He went to the mountains because it was there he wished to die, since die he must.

This was in 1873. Dr. Trudeau died in 1915 after having revolutionized the treatment of tuberculosis, brought life and hope to the hopeless and received the homage of the world.

And so the tales of inspiration might go on; were we to allow ourselves this pleasure we would require a volume rather than a few pages. Some tread the path of sorrow and adversity, coming out at last into the glorious sunshine where their footprints, like those of the dinosaur, will endure through history. Others start out under a smiling sun which marks a path both straight and clear but ere their personalities have gained sufficient weight for their footsteps to make an impress deep enough to last, the storm clouds break and disaster overtakes them. Others, less spectacular, just plod along under benign skies and, chiefly because of the straightness of their paths and their avoidance of rambling, they at length reach the pinnacle, there to plant the standard, symbolic of their contribution, great or small, toward the welfare and advancement of mankind.

But we cannot resist the temptation to write farther of one who, at the apogee of success, considered himself in one respect at least a failure. So far the world has not granted him his self-condemnation. Posterity will be the better judge.

James MacKenzie considered himself a plodder. From his own description his preliminary education was none too fortuitous. He had no patience with an educational system whose chief or only criterion of ability or scholarship was a capacity for memorizing. He would have preferred a system designed more to develop the faculties of reason. After a medical school career which seems to have been characterized neither by brilliancy nor torpidity he entered general practice. As with Sims, a patient died. This was the turning point and the starting point of MacKenzie's career.

A pregnant woman with heart disease died suddenly and unexpectedly during labor. Why could he not have foretold the dangers in this case? MacKenzie went to his books and to the learned men of the time but an answer was not forthcoming. Plenty information could he get on the character of the heart lesion and of heart lesions in general but as to prognosis and as to what lesions shall be considered of serious import and which of little consequence there was nothing to be told. MacKenzie set himself the task of finding out and, through years of painstaking study and carefully kept clinical records, following his patients from the earliest inception of a disease, through the years to its final outcome, he gradually developed the modern science of clinical cardiology. He revolutionized our concept of heart disease.

He, like George Harley, moved into Harley Street, but late in his career after his reputation had been well established.

MacKenzie went from little Burnley to great London, not that he might be a specialist, for he detested the term, but that through closer contact he might convince the reactionaries in medicine of the necessity for reorganization of their viewpoints on heart disease. Here he found himself coerced, against his will and in spite of his protestations, into the position of a heart specialist. In London he built a great new school of cardiology but he despised the distinction and implored his students to return to general practice as the only place in which chronic disease may be studied in its incipiency and followed to its termination. It was in the milieu of general practice that he confidently expected the great clinical advances in the medicine of the future. So we see an old man disheartened by the failure of his pupils to consider seriously his entreaties, determined that if none other will go, he at least must follow the light, moving his home once again, this time to the little town of St. Andrews in Scotland, there to take up again the study of disease from the viewpoint of the general practitioner.

There the great Sir James MacKenzie passed most of his later days, interested and active to the end in the work of the St. Andrews' Institute for Clinical Research which he had founded for the perpetuation of those viewpoints and ideas which he had striven so hard to inculcate.

In his work, Sir James developed a machine. Others bestowed upon it his name. This was the MacKenzie Ink Polygraph. It brought him great renown. The satisfaction of recognition was, however, deeply tempered by

the knowledge that in the minds of many it was the instrument that was worshiped and not the increasing knowledge made possible through its use. In nearly all his later contributions he did his utmost to counteract this tendency by stressing the desirability of using precision instruments only so that one may be better equipped to diagnose and treat diseases of the heart without them.

What will posterity have to say of Sir James MacKenzie? Will he, like Boerhaave and Osler, go down as one of the clinicians of his time, a prolific writer, a man to whom the world made pilgrimage, but who has contributed no truly great outstanding stepping stone to the progress of medicine? The principle of the reflex are still remains in the balance. The exhortation to study disease in its lair is evangelistic but dies with the man and is perpetuated only in as far as his personality is built into his writings. The prominence and influence of the MacKenzie Institute will be dependent entirely upon the greatness and the vision of the minds that will inhabit it.

Nevertheless we venture to believe that MacKenzie's advancement of our knowledge of cardiology, quite aside from his work with the polygraph, will assure the passage of his name through many generations of the followers of Hippocrates.

—*W. T. V.*

STEELE GLASS COMPANY
HARRIS COMER
PHILADELPHIA, PA.
622 LOCUST STREET.

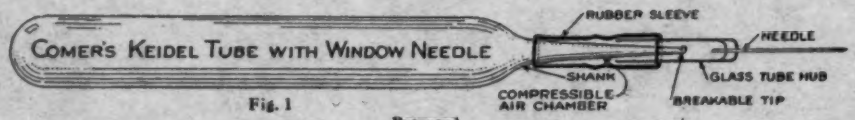


Fig. 1

Patented

Comer's Window Needle *makes it possible to SEE that*

- The breakable tip of ampoule is not prematurely broken.
- The Blood shows in Glass Hub when needle is properly introduced into vein.

This eliminates the sight unseen features of the Original Keidel Tube and will make much more certain the obtaining of good blood samples.

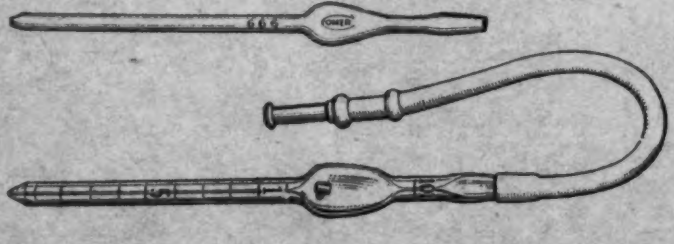
We offer also—

BLOOD CHEMISTRY KEIDELS

with Sodium Fluoride as used by the Pennsylvania Department of Health under the direction of Dr. John L. Laird

---

omer *This trade-mark on the back of our Blood Count Pipette means that we guarantee a Greater Accuracy than is required by the U. S. Bureau of Standards.*

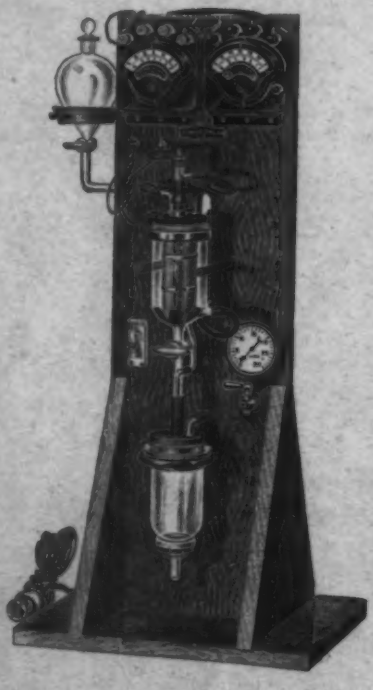


HARRIS COMER, Trading as Steele Glass Company

622 South Washington Square - - - - - PHILADELPHIA, PA.

We make apparatus of Glass for Chemical, Medical, and Experimental Laboratories.
Forty Years Experience.

BRONFENBRENNER APPARATUS



A Simple Electro-Ultrafilter

(See Jour. of General Physiology, Sept. 20, 1926, Vol. X, No. 1, pp. 23-26.)

Combines ultrafiltration with electrophoresis. Used for freeing colloidal solutions of electrolytes, dialyzing solutions containing bacteriophage, and for similar work. Capacity about 25 cc.

The author describes the performance of the apparatus as follows: "When 20 cc of broth were placed in the dialyzing chamber and the full current was turned on, the ammeter read 4.5 amperes. If this amount of broth were dialyzed without current, it would require 3 hours to increase its resistance to the passage of current sufficiently to give an ammeter reading of 0.016. When dialysis was combined with electrophoresis, a reading of 0.013 amperes was reached in 45 minutes."

This ingenious design, utilizing both the front and back of the support, results in an apparatus in which twenty-eight parts, including electrical instruments, shaking motor, etc., are combined into one complete unit ready for immediate operation on direct current.

Write for descriptive literature and prices.

EIMER & AMEND

Est. 1851 Inc. 1897

Headquarters for Laboratory Apparatus and Chemical Reagents

Third Ave., 18th to 19th St. NEW YORK, N. Y.